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INVENTORS' VIGNETTES:
SUCCESS AND FAILURE IN THE DEVELOPMENT OF MEDICAL DEVICES

Contractor Documents

Health Program
Office of Technology Assessment
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OTA PROJECT STAFF--INVENTORS' VIGNETTES

Lawrence H. Miike, Senior Associate
Jane E. Sisk, Project Director
Kerry Britten Kemp, Health and Life Sciences Division Editor
Steven J. Sisskind, Research Assistant

Clyde J. Behney, Health Program Manager
Roger C. Herdman, Assistant Director, Health and Life Sciences Division

Virginia Cwalina, Administrative Assistant
Carol Ann Guntow, Secretary/Word Processor Specialist
Diann G. Hohenthaner, P.C./Word Processor Specialist

CONTRACTORS

William M. Adams, Surgilite International
Perry J. Blackshear, Massachusetts General Hospital
Thomas P. Carney, Metatech Corporation
Frank R. Faunce, Emory University School of Dentistry
Robert E. Fischell, The Johns Hopkins University
Wilson Greatbatch, Greatbatch Enterprises, Inc.
Reed B. Harker, University of Michigan
Frederick W. Herr, Beckman Instruments, Inc.
Ralf Hotchkiss, Appropriate Technology for Independent Living
David Jaffe, Palo Alto Veterans Administration Medical Center
Alan R. Kahn, Consultant, Cincinnati, OH
J. Stark Thompson, E.I. duPont de Nemours, Inc.
Aran Safir, Consultant, Cambridge, MA
Edwin Whitehead, Whitehead Associates, Inc.
Sidney Wolvek, Datascope Corporation

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VIGNETTE #1
THE DEVELOPMENT OF TECHNICON'S AUTO ANALYZER

Edwin Whitehead
Chairman
Whitehead Associates, Inc.
Greenwich, Connecticut

The introduction of Technicon's continuous-flow Auto Analyzer in 1957 was one of the most profound, and even revolutionary, developments in the history of medicine. Based on the techniques developed by Leonard Skeggs, the Auto Analyzer totally changed the character of the clinical laboratory, allowing a literal explosion in the number of laboratory tests performed--a hundredfold increase over a 10-year period.

How the invention developed and proliferated is an interesting story. In 1950, Dr. Alan Moritz, chairman of the department of pathology at Case-Western Reserve University and an old friend of mine, wrote me to say that a young man in his department, Leonard Skeggs, had developed a most interesting instrument that he felt we, Technicon as a company, should like to develop. Since I was out of my office in New York on a prolonged trip, my father was in the habit of opening and acting upon my mail. He wrote back to Moritz saying that Technicon was always interested in new developments and enclosed with his letter a 4- page confidential disclosure form. After that, nothing happended for 3 years. Not surprisingly, Moritz thought that Technicon really was not interested, and my father dismissed the matter as routine.

Three years later, in 1953, Tecnicon's only salesman, Ray Roesch, was visiting Dr. Joseph Kahn at the Cleveland Veterans Administration Hospital. Dr. Kahn asked Ray, "Why did you ever turn down Leonard Skeggs' invention?" Ray, who had never heard of it, asked, "What invention?" and Kahn replied,

"The machine to do automatic chemical analysis." When Ray called me up and asked me why I had turned Skeggs' idea down, I said I never heard of it either and asked him what it was. When he told me it was an idea to automate clinical chemistry, my reaction was, "Wow! Let's look at it, and make sure that Skeggs doesn't get away."

That weekend, Ray Roesch loaded a couple of pieces of crude laboratory equipment in his station wagon, and drove Leonard Skeggs and his wife Jean to New York. We set up in our laboratory a simple device consisting of a Sigma peristaltic "finger" pump to draw the specimen sample and reagent streams through the system, a continuous dialyzer to remove protein molecules which might interfere with the specimen-reagent reaction, and a Coleman Junior Spectrophotometer equipped with a flow cell to monitor the reaction. This was enough to demonstrate the validity of the idea, and we entered prompt negotiations with Skeggs for a license to the patent.

We settled on an up-front payment of $6,000 and a sliding royalty arrangement for the patent license starting at 5 percent and dropping to 3 percent after a certain volume was reached. In 1953, I estimated a potential market in the United States for 250 units. In fact, this number was reached well before the end of the second year, so the royalty payment to Skeggs for all intents and purposes was 3 percent.

Technicon, then a relatively small company but responsible for a considerable amount of innovation, did not realize what it was taking on with the Auto Analyzer. It seems that after our original "turn-down" of the project, Skeggs had made an arrangement with the Heinecke Instrument Co. and the Harshaw Chemical Co. to sell it. Both of these companies erroneously assumped that the device was a finished product and offered it on the market. Neither was able to sell one instrument over a 3-year period. This was not

surprising, as there was a considerable and expensive development process necessary. Not only did Technicon have to design the device to make it rugged and reliable, but we had to develop the chemical assay methods, which, although similar to manual methods, involved considerable refinement. Technicon spent some 3 years in product development, refining the very simple model developed by Skeggs into a commercially viable continuous-flow analyzer.

Then came the question of marketing. I recognized early in the game that the traditional marketing techniques common at that time for laboratory instruments would never fly with something as revolutionary as the Auto Analyzer. At the time, the average laboratory instrument was sold primarily from a specification sheet showing what that instrument could do. The company essentially listed specifications, price and perhaps product benefits, and expected the instrument to sell either by a catalogue salesman or through the mail. In the case of the Auto Analyzer, we decided we had to sell a complete system--not only the instrumentation necessary but also the reagents and methods to perform an analysis.

The first problem was how to introduce technology as radical as the Auto Analyzer into the very conservative marketplace of the clinical laboratory. It was at this point that we decided to do clinical evaluations. Such evaluations have become commonplace today, as demanded by the Food and Drug Administration (FDA). However, Technicon's clinical evaluations protocol for the Auto Analyzer contained a few twists not in common use today. Specifically, we insisted on the following three techniques:

- o 100 samples run in triplicate, both by manual and automated technique to prove precision of results.

- o An extensive series of recovery experiments by both techniques. (In recovery experiments, a known amount of material is added to a serum sample. In a perfect world, the analysis of this sample will produce the exact amount of material added.)
- o Correlation experiments with the existing laboratory.

It was in correlation experiments with existing laboratories that we ran into considerable difficulty. As manual results at the time were notoriously imprecise, the Auto Analyzer results rarely, if ever, agreed with the laboratory results. A few laboratory directors were very upset and cancelled further testing. Fortunately, however, more directors were willing to accept, and in fact endorse, the Auto Analyzer.

The most unusual condition of the evaluations of the Auto Analyzer was Technicon's insistence that the laboratory call a meeting of its local society to announce the results. Such meetings generally resulted in an enthusiastic endorsement by the local laboratory director, whom we picked for his or her prominence. I believe this technique had an enormous amount to do with the rapid market acceptance of the Auto Analyzer.

Perhaps I have glossed over the 3 years from demonstration of feasibility to production. Because of the radically different nature of the technology, a number of problems had to be overcome that were quite unique to the process. For example, the principle of the Auto Analyzer, as opposed to any analyzer preceeding it, was to pump a continuous-flow stream of reagents interrupted by specimen samples. One basic problem, therefore, was the interaction of specimen samples. For the most part, this problem was solved by the introduction of air bubbles between the samples to act as physical barriers between the samples. To some extent, however, the problem of "specimen carryover" is almost inevitable in a system like this, being greatly

affected by the formation and size of the bubbles, the configuration of the dialyzers, the inside diameter of the tubing through which the fluids flowed, the temperature of the heating bath, the pattern of peristaltic pumping action (suck-back), etc.

The entire Auto Analyzer project was financed internally at Technicon. The company had ongoing business at the time with automatic tissue processors for histology laboratories, slide filing cabinets for such laboratories, automatic fraction collectors for chromatography (we were the inventors), and chest body portable respirators for polio patients--the total business in those days was probably less than $10 million. Even so, Technicon had an unbroken record from 1939 to 1969, when it went public, of never borrowing money nor selling any equity. Thus, the entire Auto Analyzer project, which was enormous for a company of Technicon's size, was financed internally with no borrowing or any outside funding of any type.

The patent on Skeggs' original invention was central to the development of the Auto Analyzer. Without a patent, Technicon would never have pursued the development of this device. The development of the Auto Analyzer was far too expensive to allow a competitor to copy Technicon's device with no development expense and to share the market.

The patent was challenged in the middle-1960s by the Coleman Co., now a subsidiary of Perkin-Elmer. We had a difficult decision to make in that although Coleman advertised the product, they never delivered one. Our decision was whether to test the patent in court before Coleman's product was on the market and being used or to wait until the product was on the market.

Technicon made the decision to prosecute immediately, at considerable expense. Fortunately, we had a complete victory, the judge finding for us at every point of contention. As is well known, a court-tested patent is an

extremely strong defensive weapon. The patent was never further challenged throughout its life, and it was only after the patent expired that a number of copies of Auto Analyzers appeared on the market, mostly in Europe.

In connection with the Auto Analyzer, Technicon encountered extraordinary expenses for the following:

- o Symposia the world over.--About 25 symposia were held in most of the major countries of the world including the United States. The symposia were generally 3-day affairs, attracting between 1,000 and 4,500 scientists. They consisted entirely of papers and exhibits on techniques in automated analytical chemistry and became major scientific events throughout the world.
- o Training classes.--Technicon realized early on that with an instrument as radically different as the Auto Analyzer, market acceptance could be irreparably damaged by incompetent users. Accordingly, we set up a very broad-scale training facility. Technicon insisted that every purchaser of an instrument come to our training centers around the world for a 1-week instruction course. My estimate is that about 50,000 people have been trained on Auto Analyzers. Thus, a certain degree of competence, along with great product loyalty, was built up among users.
- o Expensive and at the time very unusual service policies.--Technicon guaranteed 24-hour service at any location in the world. We accomplished this by various means.

It is my belief that without these, at the time extraordinary, techniques, Technicon never would have achieved the success of the Auto Analyzer. Without a strong patent position, however, there is no way we could have made the expenditures required for the Auto Analyzer's success.

The amount of protection offered by patents is in my opinion, considerably less today than it was before the advent of FDA. Compliance with FDA regulations causes a delay in product introduction that can amount to, literally, years. The reason is simple. In order to get valid FDA information, one has to have a finished system. Therefore, FDA submissions occur at the end of the product development cycle rather than during it. Patenting on the other hand, occurs at the beginning of this cycle. Therefore, any time taken with FDA submissions directly reduces the length of time for a patent monopoly. Thus, I believe that Congress should pass legislation adding to the effective life of a patent for a product or process that is subject to FDA regulation.

The Auto Analyzer was developed long before the expansion of FDA's regulation of medical devices by the Medical Device Amendments of 1976. By and large, Auto Analyzers have required only 510(k)B filings and conformity to Good Manufacturing Practices. Although many of Technicon's middle-management people feel very put-upon by FDA regulations, as top management, I feel that FDA regulation has probably had a beneficial effect on our business. Our manufacturing processes and quality control are more stringent, and we are considerably more cautious in our labeling.

Federal tax and investment policies really did not affect the development of the Auto Analyzer except as mentioned above.

Technicon's marketing strategy for the Auto Analyzer has always been promotion through professional meetings, scientific papers, journal articles, etc. A professional selling approach has always been used. Technicon primarily employs only direct salesmen. The company has never used agents or distributors, except in certain small countries where the markets are too small to support direct sales.

The foreign market is and always has been an important part of Technicon's efforts. Exactly the same sales strategies are used in foreign markets as in the U.S. market (direct sales, scientific papers, symposia, meetings, etc.). Although there are tariff barriers to trade in many countries, there are also significant nontariff barriers in most places. In Japan, for example, a foreign product must qualify for the Japanese market if it sells for more than $80,000. The requirements are quite stringent and generally delay market introduction. In France, we often sell to the Government, and the French Government has a definite policy of buying local products in preference to imported products. In Great Britain, our single customer is the Ministry of Health. Here again, there is a British policy that every effort is made to hold down purchases from America as opposed to purchases of British-made products.

Technicon currently has sales offices in 23 countries and distributes in, I believe, a total of 68 countries. The foreign market for Auto Analyzers represents in excess of 50 percent of the total market.

When we started the development of the Auto Analyzer in 1953, I estimated a potential market of 250 units. Currently, in excess of 50,000 Auto Analyzer Channels are estimated to be in use around the world. The difference between the projected and actual market was due to our trying to approximate the 1953 market for laboratory tests. Since 1953, the number of tests performed has increased logarithmically, largely as a result of the availability of automation.

In reviewing the 35-year history of Technicon's Auto Analyzer, I have come to the conclusion that several factors signficantly influenced our success. First, the Auto Analyzer allowed both an enormous improvement in the quality of laboratory test results and an enormous reduction in the cost of

doing chemical analysis. Second, there was a realization by physicians that accurate laboratory data are extremely useful in diagnosis. And finally, reimbursement policies, both in the United States and abroad, increased the availability of health care.

VIGNETTE #2
THE STORY OF TECHNICON'S SMA 12/60
(SEQUENTIAL MULTIPLE ANALYZER, MODEL 12/60)

Edwin C. Whitehead
Chairman
Whitehead Associates, Inc.
Greenwich, Connecticut

By 1960, most of the larger hospitals in the United States were using Technicon's Auto Analyzer--the revolutionary new instrument based on the continuous-flow techniques developed by Leonard Skeggs (see Story #1). Furthermore, the laboratory test load in these hospitals was increasing dramatically, probably 300 percent a year. Two things became apparent. As the difficulty of performing clinical laboratory tests diminished and the quality of the results increased, the laboratory's workload expanded.

Leonard Skeggs' at this point was in the habit of visiting Technicon in New York at least once a month. Since Skeggs came from Cleveland, he would generally stay over night, usually in my home. He and I would frequently stay up late at night talking. During one of our late night talk sessions, Skeggs and I made the observation that the cost of performing a chemistry test by automation had dropped from about $5 to something on the order of 2 cents. We also noted that the true cost of doing a test was not in performing the analysis, but rather in collecting the blood, separating blood from plasma or splitting the blood sample into aliquots (parts) for different analyses, collating the results for a particular patient, and getting the results back to the patient's chart. The smallest and least costly part of all this effort was in actually performing the analyses with an automated machine. Skeggs and I reasoned that as long as one was going to all this trouble, one should derive the maximum amount of information possible without adding to the cost.

Thus was born the concept of continuous-flow analyzers capable of performing multiple analyses.

Shortly thereafter, a well-known clinical biochemist by the name of Ralph Thiers at Duke University decided to conduct an experiment. He wanted to know how much unsuspected medical information would be derived if every patient coming into the hospital were provided with a chemical profile. For that reason he came to us at Technicon, and we put together 11 separate Auto Analyzers so that he could perform 11 tests on every incoming patient.

Thiers performed the tests on some 2,500 patients entering Duke Hospital. His results showed that in the ordinary course of events, 150 patients per 1,000 admissions had significant blood chemistry abnormalities that were picked up by the routine hospital laboratory. Thiers' "automation" laboratory, however, picked an additional 210 patients per 1,000 with significant abnormalities that did not show up in any tests requested by physicians. In other words, 210 patients per 1,000 would have been admitted and discharged from Duke Hospital without having had significant blood chemistry abnormalities detected.

Theirs' results, which were published in the Journal of the American Medical Association, had a considerable effect. Although many physicians resented the implication that they would miss so many cases, many others picked up the idea and a certain "ground swell" of desire to perform admission profiling was established.

I neglected to mention that Duke assigned medical residents to analyze the data in order to find out the true significance of the abnormal findings detected. Obviously, this was an enormously difficult and painstaking task. However, after going through a large number of patients charts and interviews, etc., the investigators came up with the statistic that in 5 or 6 percent of

cases, the information produced by the automation laboratory resulted in a change of diagnosis for the patient.

In the meantime, Technicon had been working on a multiple-analysis machine whose name, Sequential Multiple Analyzer (SMA) was descriptive of the technique employed (i.e., sequential multiple analysis). A conventional Auto Analyzer at the time consisted of a sampler, dialyzer, heating bath, detector (either a colorimeter, fluorimeter, a flame photometer, or other detector), and a recorder. The concept underlying the SMA was that there would be a single sampler to aspirate the specimen sample into the system, and the sample would be split into segments for different analyses. The air-segmented streams of samples and reagents, would be moved through the system by pumps to analytical cartridges (one for each type of test), where the chemical reaction would occur. The multiple test results for each specimen would record on a single recorder.

Technicon put together the first experimental continuous-flow multiple-analyzer, an eight-channel affair, to prove the idea and apply for patents. We then went to the field and asked what tests should be included in a multiple-channel analyzer. The field expressed unanimity on the need for about six of the tests, but held widely varying views on what other tests should be included. Technicon then made a fundamental decision which enormously accelerated our research. We made sure to include the important six tests and then did the tests that were most easily accomplished.

Finally, in 1963, Technicon put its SMA 12/30 instrument on the market. This 12-channel machine did 12 tests per sample at a rate of 30 samples an hour and sold for $30,000. The SMA 12/30's success was somewhat limited because of the difficulties in operating the instrument. Phasing (i.e., allowing the tests to appear sequentially one after another) in the SMA 12/30

was accomplished by using a trombone-like mechanism to increase or decrease the fluid path length each analysis train pursued. The trombone-like apparatus proved to be very difficult to adjust and extremely fragile to use.

In 1966 or 1967, Technicon introduced the next generation instrument, the SMA 12/60. This machine was a vast improvement over the 12/30. It did 12 tests per sample at the rate of 60 samples an hour and was far more reliable that the SMA 12/30. There were two reasons for the SMA 12/60's greater reliability. First of all, instead of using fluid path length for phasing, we stored all results electronically and spat them out when the last test was performed. Second, having discovered that an irregular pattern of air bubbles in the fluid stream caused a considerable amount of extraneous "noise," in the SMA 12/60, for the first time, we actually pumped air into the fluid stream rather than allowing it to be sucked in. This technique provided an extremely uniform bubble pattern and allowed results to be pumped out at the rate of 60 samples an hour.

Pricing Technicon's SMA 12/60 became an extremely ticklish operation. Our goal during development was to design the product so that it would be profitable with a targeted sale price of $40,000. After we finished the development of the SMA 12/60, however, my father, quite irrationally it seemed to me at the time, insisted that we sell it at $60,000. With the $40,000 price, we had anticipated a market of approximately 500 units. This new offering price made me terribly uneasy, because up until that time, clinical laboratories had never spent anything like $60,000 on any single piece of equipment. So I devised the following strategy.

Instead of trying to sell the SMA 12/60 system outright, we approached the laboratory with a metered rental plan. Under the rental plan, Technicon would install a meter in the machine and charge the hospital for usage at the

rate of $2.50 a sample. My strategy at the time was to sell the hospital's pathologist on the idea that he or she could charge $15 or $20 for the 12 tests, since the tests performed individually and manually were billable at $5 each. I reasoned that the pathologist would immediately see a profitmaking opportunity in paying $2.50 to Technicon and keeping a large part of the balance of the billed charge as profit for the hospital. A decision about renting the SMA 12/60, of course, would depend on the hospital administrator's approval. The pathologist would take Technicon's salesperson to the hospital administrator, and the administrator would probably ask how many samples one could reasonably expect to run. Since most hospitals would run in excess of 100 samples a day, the administrator would quickly see that the hospital would be paying at least $1,250 a week for the rental. The administrator would then ask how much the SMA 12/60 costs, and the $60,000 purchase price would look very attractive compared with the rental, and we would sell the systems.

In practice, this strategy worked out. The SMA 12/60 system was greeted enthusiastically. However, many hospitals were strapped for capital and welcomed the metered rental plan. In any event, the strategy provide exceptionally acceptable and the 12/60 system prospered.

In the mid-1970s, the SMA 12/60 was succeeded by Technicon's computer-controlled instrument known as SMAC (Sequential Multiple Analyzer Plus Computer). The SMAC instrument did 20 tests on each sample at the rate of 150 samples an hour. Two advances over previous instruments allowed this great increase in speed.

In Technicon's earlier continuous-flow instruments, air bubbles in the tubing had to be physically removed immediately before the fluid stream passed through the sensor, because otherwise the air bubbles would cause considerable distortion of the recording. In SMAC, we were able to pass the air bubble

through the sensor and to suppress the signal from the air bubble electronically with the aid of the computer. This electronic debubbling improved the "wash" (or reduced contamination) from sample to sample and allowed a great increase in the instrument's speed. The second major advance was a use of the computer in SMAC to collate, correct, calculate, and provide automatic quality control on the results of the instrument.

SMAC was introduced to the market at price of $150,000, and a metered rental plan was available. The instrument has achieved considerable success and in fact today is the backbone or workhorse of most large clinical laboratories. The operating costs for such a machine are almost trivial, and over time, the capital costs for such a machine become trivial as well. The average SMAC today processes more than 300 samples a day, and many instruments get up to 1,000. Thus, amortization of the system is very rapid.

Around this has evolved the work station philosophy of Technicon. Today the major expense of a clinical laboratory is labor. Depending on the volume of tests run, this expense ranges from 40 percent to 65 percent of the laboratory's total budget. Thus, if one truly wishes to cut down the cost of operating a laboratory, the first place to attack is labor. It is our contention that the true way to attack labor is to cut down on the number of work stations or, stated another way, to increase the number of multichannel analyzers.

Since SMAC is probably the most expensive and performs the greatest number of tests of any instrument in the average hospital, we use it as an example. The cost per sample for all 20 tests on the SMAC instrument is about 40 cents. It is our contention that if even 1 of the 20 available tests is requested, it is economic to run the SMAC for that 1 test, as the incremental cost is 4 cents and the increased labor cost is probably not measurable since

the system turns out 150 samples an hour with a single technician. If a work station were devoted to only that single test, and the SMAC replaced some 20 work stations, the laboratory would be saving a considerable amount of money by performing single tests on the SMAC.

To prove this point, we did a study at Montefiore Hospital in New York which runs a combined laboratory with the Albert Einstein School of Medicine. In the 10-year period from 1965 to 1975, the laboratory's budget, measured in constant dollars, remained static. During this 10-year period, the number of tests performed increased tenfold, and the number of patients served by the laboratory increased fivefold. The more significant figure is probably the increase in the number of patients served. Although performing all tests on every sample would increase the number of tests, the fact that the laboratory served five times the number of patients at no increase in price is very dramatic evidence indeed. During this 10-year period, the number of work stations in the laboratory decreased equally dramatically, and the number of multichannel analyzers, of course, increased.

The invention of multiple analysis was certainly an in-house joint effort. I believe there were some five individuals, including myself, named as original inventors. The patent on the basic idea of sequential multiple analysis has stood up well since 1963. There have been no infringers or even "close to" infringements. Once again, the development of this idea never could have been undertaken without the patent protection offered. During the early years of sequential multiple analysis, the air bubble and dialyzer patent of the Auto Analyzer pertained, but these ran out in the mid-1970s and still no competitors appeared.

SMA 12/60s and SMACs are in operation all over the world. I believe some 500 have been exported, and one finds them operating in such remote areas as Singapore, Hong Kong, Malaysia, all of the Arab countries in the Middle East, as well as in Israel, most of Latin America, etc. This is an enormous tribute to the perceived value of the SMA instrument, as it is quite a complex piece of equipment and the service problems in these remote areas are overwhelming. In these remote areas, we insist that not only operators of the system come to a Technicon central laboratory to learn its operation, but also the mechanical and electronic technicians from the institutions come as well to learn to service the device. Today, it is certainly known and respected all over the world and performs a vital role in export of American technology.

The SMA family of instruments face considerable nontariff barriers to trade in many countries of the world. In most countries, the instrument must comply with regulations similar to those of the U.S. Food and Drug Administration. Since there is no international body, one must qualify country-by-country. Pity the small manufacturer who does not have the resources to comply with these regulations. Often the markets are too small to permit special qualifications. Further, in some countries like Japan, the product must go through a long evaluation process. It is my understanding that the qualification process for Japanese companies is much less protracted than the process for foreign companies.

The development process for the SMA 12/60 was an evolutionary one and quite orderly. It was funded entirely by internal funds. In fact, until 1969, when Technicon became a public company and I sold 5 percent of the equity, Technicon had never borrowed money from any source nor sold any equity. Furthermore, Technicon had never received any funding from outside sources for any of its developments, despite repeated opportunities to obtain

funds from the National Institutes of Health as well as National Aeronautical and Space Administration and the Department of Defense. The reason for not accepting Federal funding was very simple. We never accepted a penny because of the patent policy of these granting agencies. It was only recently, when the U.S. Government changed its policy to allow limited patent rights to inventions developed in part with Federal funds, that our company would even consider Government funding. Technicon has always believed that patents are fundamental to its strategy. The cost of development as well as the cost of product introduction is so huge in the clinical chemistry instrumentation field that without patent protection, our company would not embark on product development.

VIGNETTE #3
DUPONT'S ACA (AUTOMATIC CLINICAL ANALYZER)

J. Stark Thompson, Ph.D.
Director, Diagnostic Systems Division
Biomedical Products Department
E.I. duPont de Nemours, Inc.
Wilmington, Delaware
and
Thomas M. Craig[1]

INTRODUCTION

The brilliant ideas that spawn new technological developments are often born in unusual ways. Thus, for example, Don Johnson, now a director of research and development (R&D) for new products at DuPont, found the solution to a difficult technical problem in clinical analysis while sipping a milkshake at a fast food restaurant. That discovery is one example of how solutions were found during the development of DuPont's Automatic Clinical Analyzer (ACA). The ACA is a computer-based, discrete-sample clinical laboratory analyzer that automates a wide variety of tests on blood serum and other body fluids. Unlike continuous-flow analyzers, the ACA can perform all or only one of a variety of tests on each blood sample that is processed.

The heart of the instrument is a disposable envelope or test pack, which contains prepackaged reagents necessary for each test. The instrument injects the specimen sample into the individual test pack, performs the analysis, and prints results. Test results, available within minutes, are used as an aid to physicians in making and confirming diagnoses.

ORIGIN

[1] Thomas M. Craig died in August 1986. At the time of writing, he was the Manager for Market Development, Clinical and Instrument Systems Division, Biomedical Products Department, E.I. duPont de Nemours, Inc.

Dupont's entry into the field of medical instrumentation evolved from a $1.9 million project designed to put the company into the instruments business. In the early 1960s, having gained a foothold in the instruments business with the successful commercialization of two instruments originally developed for in-house company use--a process analyzer developed by the Engineering Department, and a differential thermal analyzer developed by the Plastics Department--Dupont was ready to expand its instruments line. Therefore, an R&D program was established to evaluate new fields of interest and to propose new instruments for development.

Don Johnson, who was a manager for new products in the Instruments Products Division, reviewed several fields of analytical intrumentation, including chromatography, X-ray, spectral analysis, and various aspects of automated wet chemistry. Finally, after consultation with Dr. G. Phillip Hicks and Dr. Frank Larson at the University of Wisconsin, a decision was made to begin a program on the development of new flow technology for the automation of wet chemical analyses. Wet chemical analysis was believed to hold great potential in the analytical laboratory.

Having decided on an area in which to concentrate, DuPont's Instruments Products Division brought together a small team of scientists to work with Hicks to develop an instrument for continuous-flow enzyme determinations that would incorporate his differential photometric approach. The team's first approach was to pump streams of specimens and reagents through tubing linked to DuPont's already commercially available photometric process analyzer. After several months work, however, it became apparent that important technology in this area was already covered by patents. Various other approaches were considered, and the team struggled for weeks to get around this impasse.

BREAKTHROUGH

The breakthrough came in August 1964, when the scientists proposed abandoning continuous-flow methods and instead performing discrete- sample analysis (one test at a time, in any order) using prepackaged chemistry tests. At the time, hospital chemical analysis intruments were geared for large batches--running the same test on 50 or 60 patient samples at a time. Analyzers could not be operated economically to handle the small batch, special, and emergency ("stat") tests and night work. These tests, which had to be done manually, constituted only about 30 percent of the total volume of lab work, but accounted for approximately 90 percent of the lab's total labor and material resources. The idea of discrete analysis through prepackaged chemistry tests seemed to offer a means of automating individual specialty and emergency tests, as well as small batches of routine tests.

"During our discussion of this proposal," Johnson recalls, "we considered metering liquid reagents into test tubes that would virtually march down a line in the intrument. This had already been tried, however, and we realized that there would be too many problems with the idea. The process seemed messy, and, at the same time, it would be difficult to quickly change from one method to another. Stored liquid reagents also made the maintenance of calibration a problem."

In continuing technical discussions, there evolved the concept of using a plastic bag to contain prepackaged reagents and to serve as the reaction chamber for each type of test performed on a given blood sample. This idea was to prove central to the development of the ACA.

DESIGN

Disposable Test Pack. One of the first design problems that arose in connection with the ACA was how to design the disposable reagent-reaction test pack so that the enclosed reagents could be mixed with the patient blood sample. The pack that was finally designed by DuPont's engineers had a row of pods at the top to contain the reagents for a specific type of test. During processing, as a result of hydrostatic pressure from within the pack, the chevron-shaped seals of the pods would break open, releasing the reagents into the interior of the test pack, where they would be mixed with the blood sample.

For some tests, a chromatography column was required to remove interfering material from the sample. Another problem that arose, therefore, was how to perform column separations within the self- contained test pack. The inspiration for solving this problem resulted from Don Johnson's thirst. "We knew that we needed a low-cost, disposable chromatography column, but had not been able to find tubing with the necessary combination of properties," Johnson recalls. "While I was on vacation, I stopped at a fast food place and ordered a milkshake. The shake was served with a thin plastic straw that is so commonplace nowadays. I realized that this might be used as the column in the test packs." Thus, Johnson returned home from his trip with samples of the straw, and a commercial straw company was contracted to customize some of these novel polypropylene straws for use as small chromatography columns in certain test packs.

In the search for a material to make the actual envelope of the test pack, DuPont's engineers examined and tested wide variety of materials. One requirement was that the material be able to form temporary seals (for the reagent compartments) as wells as a permanent seal (for the outer perimeter of the pack). Finally, DuPont's background in plastics proved helpful. The

material that was finally selected was "Surlyn" ionomer resin, a resin the company had recently developed which could be processed into a plastic film with unique properties. Among Surlyn's characteristics were toughness, the ability to be molded and extruded precisely, and transparency (even into the ultraviolet range), and the ability to form a peelable heat seal.

Reagents. Another big problem was how to store the reagents in the test pack. Several approaches were tried without success. Finally, the idea of using fast-dissolving tablets, an idea borrowed from the pharmaceutical industry, was proposed.

According to Johnson, the team of scientists subsequently decided to pay a visit to a pharmaceutical company. "The physical pharmacists told us they could develop tablets that would dissolve in 1 to 1+ minutes. That was simply not fast enough. We wanted a tablet that would dissolve in 5 seconds. Also, they told us the accuracy of thier tablets would be no better than 5 percent. That also was not good enough for us. We wanted accuracy of better than 1 percent. So, we went back to the drawing board to design the tablets and even the tableting machinery ourselves."

Once again, DuPont's experience in other areas proved helpful. The scientists discovered that DuPont had a fast food freezing process that could be adapted to produce uniform free-flowing powder mixtures that could then be made into very uniform tablets. The adaptation of this process allowed precise quantities of reagents, in their optimally stable form, to be stored for extended periods in the packs and then be released in seconds to perform their individual roles in a diagnostic assay.

Instrument Design. In late 1964, DuPont's engineers began work to develop the first of a series of prototype instruments that would bring the reagent-reaction test pack, the reagents, and the blood samples together for automatic processing.

Prototype I embodied, in a rough form, almost all of the capabilities of the final instrument. Blood samples and reagent-reaction packs for any test desired on the sample were manually placed in an input tray to be conveyed to the analyzer. The entire system was built around a turntable, which carried the test packs through a series of stations for specific operational steps. Although the packs were placed on the machine manually, the actual analysis was performed automatically.

In early 1966, barely a year after Prototype I was begun, DuPont's entire executive committee visited the tiny laboratory in Wilmington to review the progress of the project and see the instrument in operation. The machine processed 200 packs without a malfunction, and the committee decided to approve the project's continuation.

Prototype II, developed during 1966, encountered an unexpected problem. Beacuse the instrument pushed test packs along rails and up elevators, getting the packs to the various operating stations was complicated and awkward. "It was a very cumbersome method," Johnson recalls. "Too much was happening in a small space, and it just did not work very well. Although Prototype II had pack loading and unloading capabilities and successfully performed photometric analysis, it was a mechanical monster. So after a traumatic meeting in October 1966, we decided to go back to the drawing board--again."

In 6 weeks, the engineers had devised a solution--a simple gear-driven bicycle chain that would carry the packs on a continuous journey through the instrument and around the various stations. The engineers also devised an improved system to inject the correct amount of blood serum and a diluting agent into the individual test pack. Like the original prototypes, Prototype III performed the photometric measurement on the serum-reagent mixture in a precise optical cell that it formed in the plastic test pack. However,

Prototype III had improved photometric accuracy approaching that of the National Bureau of Standards. It also had the ability to process test packs in random order and to identify each test and patient sample on the automatically printed report slip. The scientists decided it was time to obtain an independent evaluation of the system's capabilities, and a duplicate of Prototye III was built for this purpose.

EVALUATION AND COMMERCIALIZATION

A working prototype of the ACA was sent to the University of Wisconsin Medical Center for 7-month evaluation of its accuracy and reliability and for comparison with existing methods of clinical analysis. Two other major field evaluations were conducted at the Upstate Medical Center in Syracuse, New York, and at the University of Alabama Medical Center.

The information from these evaluations was widely disseminated for study by clinical laboratory personnel. Those involved in the study at the University of Alabama published a monograph, and those involved in the Syracuse evaluation published an article in the Journal of Clinical Pathology. Dr. Merle Evenson of the University of Wisconsin Hospital's clinical chemistry laboratory presented his evaluation of the ACA at the 1968 National Meeting of the American Association for Clinical Chemistry. The instrument was formally introduced at that meeting, and according to Don Johnson, "It was the hit of the show."

By 1970, when the first commercial ACA was shipped, a number of technical problems with pack manufacture, pack leakage in the instrument, and instrument reliability had been overcome, and the ACA had the high quality and accuracy that guaranteed its success in the marketplace.

MARKETING

By designing the ACA to automate specialty and emergency tests, as well as small batches of routine tests, DuPont carved a niche for the ACA in the clinical laboratory. The ACA is marketed to complement large batch analyzers in medium and large hospitals and to serve as a total chemistry laboratory in small hospitals, clinics, and group practices where patient batches are usually small. Currently, the ACA is used by more than 4,500 hospitals worldwide to increase the speed, efficiency, and accuracy of clinical analysis. In 1983, DuPont's sales of clinical analyzers and test packs in the United States and abroad were approximately $300 million. Most of this revenue is from ACA sales in the United States, although some of it is from sales of analyzers and test packs to other industrialized countries throughout the world.

Four generations of ACA instruments have been introduced since 1971: the ACA-II, which has a solid-state computer system and a 60-channel capacity; the ACA-III, which is controlled by microprocessor technology and has virtually unlimited test capabilities; the ACA-IV, a benchtop instrument; and the newest analyzer, the ACA-V. Accessories developed for the systems now in use include a channel-expansion accessory, a computer interface accessory, and an ion selective electrode accessory for sodium and potassium assays.

Whenever a new model or accessory is introduced, DuPont takes steps to make it easy for existing users to increase systems capability. Therefore, if a laboratory wishes to, it can continue to use the same system it purchased initially, but with the increased test capacity of the newest systems being produced. In those instances in which it is not technically feasible to upgrade or retrofit a system (e.g., in going from an ACA-II to and ACA-III), DuPont's exchange program allows a fairly substantial trade-in value to minimize the cost of upgrading to existing ACA users.

Since the original ACA's introduction with eight tests in 1971, DuPont's scientists have been continually working to automate other tests. Currently, the ACA system automates over 70 specialty and routine clinical tests--more than any other automated analyzer. Among the special chemistry tests introduced in recent years are a test for the enzyme CKMB (creatine kinase MB isoenzyme), an aid in the diagnosis of heart attacks; tests for the coagulation factors anitithrombin III, plasminogen, and fibrinogen; tests for immunoglobulins used to monitor diseases; and tests for monitoring therapeutic drugs such as phenytoin, primodone, and phonobarbitol. More tests in the areas of coagulation, endocrinology, therapeutic drug monitoring, and special chemistries are expected by the late-1980s.

Because of the high turnover of personnel in clinical laboratories, DuPont provides a comprehensive training program for all ACA customers. The ACA training center, located in Wilmington, Delaware, offers both basic and advanced training programs for customers.

DuPont has also committed a large amount of resources to satisfying the service needs of ACA users. Telephone trouble shooting is an important aspect of DuPont's total service program. With the ACA user training sessions and the use of the operator's manual, trouble shooting solves 9 out of 10 problems over the phone. For problems which cannot be handled over the phone, DuPont maintains a large network of satellite service engineers, supported by regional and area service centers, that provides around-the-clock service to ACA users, thus minimizing downtime on the ACA system.

The ACA system design is modular, so parts can be easily replaced. Often, the hospital's laboratory staff can interchange the part needed to get the system back in operation quickly. To ensure that parts are available, DuPont has regional parts depots at airports throughout the country. As soon

as a problem has been isolated to a single component of the system, a service engineer can call the regional parts depot, and the necessary component will be put on the next plane, again minimizing downtime.

The ACA has a number of features that make it attractive to clinical laboratories. One of the things that sets the ACA apart from other automated analyzers is its ability to perform a number of special chemistries in addition to routine tests. Because of the ACA system's accuracy, precision, and range of linearity, expensive test repeats and duplications are minimized. Furthermore, by reducing the need for glassware and supplies, by reducing reagent waste, and by reducing the number of standards and controls required to ensure accuracy and precision, the ACA helps contain the laboratory's total cost for performing small batch testing. Also, the minimal operator involvement necessary with the ACA reduces labor costs associated with clinical testing and frees laboratory personnel to work on more challenging tasks.

Unlike large batch analyzers which run a battery of tests, the ACA allows a laboratory to run only those tests requested by a physician. Thus, the ACA avoids inefficient and often costly mass profile screening. The decade ahead will bring new advances and new technology to all areas of the hospital laboratory. DuPont's scientists will continue their efforts to ensure that the ACA possesses the latest in state-of-the-art technology and clinical testing capability.

VIGNETTE #4

BECKMAN'S ASTRA (AUTOMATED STAT/ROUTINE ANALYZER) SYSTEM

Frederick W. Herr
Business Manager
Current ASTRA Systems
Beckman Instruments, Inc.
Health Care Group
Clinical Systems Division
Brea, California

In 1970, Beckman Instruments introduced to the clinical marketplace the first dedicated instrument for dramatically improving the ease of glucose analyses. This instrument, the Beckman glucose analyzer, was simple to use, required only 10 microliters of sample, and gave the result in less than 1 minute. In addition, the method the instrument used to measure glucose (oxygen rate) eliminated most interferences found in other methods. The Beckman glucose analyzer soon became a worldwide standard for the measurement of glucose in biological fluids such as blood.

In 1971, Beckman introduced a second dedicated analyzer, this one for the measurement of urea nitrogen (BUN). Like the glucose analyzer, the Beckman BUN analyzer was simple to use, microsampled, and gave "stat" answers. The BUN analyzer used a novel rate conductivity to measure the BUN reaction. Also in 1971, Beckman introduced the Klina Flame, a modular flame photometer for the measurement of sodium, potassium, and lithium. In 1973, Beckman introduced a third dedicated analyzer, this one for the measurement of creatinine. Similar to the glucose and BUN analyzers, the creatinine analyzer was simple to use, microsampled, and gave stat answers. It also used a rate method to measure creatinine.

The worldwide users of Beckman's instrumentation began to inquire when Beckman was going to incorporate all of these technologies into one system. In 1975, using its expertise in dedicated analyzers, Beckman introduced the chloride/cargon dioxide analyzer. This analyzer had features similar to those of the glucose, BUN, and creatinine analyzers and was the first clinical instrument to measure carbon dioxide using a rate pH technique. Now the combining of these chemistries and technologies was at hand.

In analyzing the clinical marketplace in, we at Beckman determined that there were two distinct types of analyzers available to the laboratory--those that did many tests (profiling) on each sample and those that did one test at a time. When we looked at the laboratory's workload, we found that many samples requiring many tests came into the laboratory early in the morning, but from then on, most samples came into the laboratory randomly and each had different test requirements. We found no one clinical instrument that was available at that time which could effectively handle the samples comprising the bulk of the laboratory's workload. It was from this information that combining the Beckman technologies into a system called ASTRA (Automated Stat/Routine Analyzer) was begun.

In 1978, Beckman introduced two ASTRA systems--the ASTRA 8 and the ASTRA 4--which would accept 8 and 4 analytical modules, respectively. The six analytical modules that were initially available were modules for the measurement of glucose, BUN, creatinine, sodium/potassium, carbon dioxide, and chloride.

The ASTRA systems have a number of the same features as Beckman's dedicated analyzers--case of use, microsampling, and discrete analysis. The systems also have several unique features. One is 24-hour stat capability. With the push of a button, the operator can switch from the routine mode of

operation to the stat mode. One minute and one stat later, the system automatically returns to the routine mode. This feature allows a laboratory to run the majority of its samples on one system, thereby saving time and money. Another feature is proven performance. The methods used in the ASTRA are the same as those used in Beckman's dedicated analyzers, with sodium/potassium measured by ion-selective electrodes. This feature allows the laboratory to keep the same normal range which benefited the laboratory and clinician alike. A third feature is automatic calibration. When the operator pushes the calibration button, the ASTRA automatically calibrates itself, but only for those chemistries requested, thus yielding additional savings in time and money.

The combining of the unique features of the ASTRA systems with the features of Beckman's dedicated analyzers was accomplished through the use of a unique software system within the instrument. To program the ASTRA system, we initially chose an Intel 8080 with 16 kilobyte memory. As we have added new chemistries to the system, we have had to expand the memory capacity to 64 kilobytes by going from EPROMs (electrically programmable read-only memory) to floppy disks. The ASTRA, therefore, was simply the product of taking existing Beckman technology and controlling it through a microcomputer.

Since the introduction of ASTRA in 1978, Beckman has introduced several additional chemistry modules. These include total protein, albumin, calcium, amylase, total bilirubin, direct bilirubin, cholesterol, triglycerides, uric acid, phosphorous, and six enzymes (ALT, AST, GGT, LD, CK and AP)--a total of 23 chemistries. Marketing of these modules was approved by the Food and Drug Administration (FDA) via the 510(k) notification process established by the Medical Device Amandments of 1976.

A unique part of the ASTRA is the enzyme module. Up to three enzymes can be run on a single module. There is as much software used to control the enzyme module as there is in the rest of ASTRA. The enzyme module was a major development project for Beckman.

At the heart of the enzyme module is a carousel with 15 semidisposable plastic cuvettes (small laboratory vessels). Liquid reagents contained in cartridges on the module are delivered accurately and precisely into the cuvettes by means of dispensing syringes. Between patient serum samples, old reagent is aspirated away and the cuvettes are rinsed by means of a set of peristaltic pumps. The carousel contains rinse solution in idle, but as soon as the run/start button is pressed after programming, the proper reagents are dispensed into the appropriate cuvettes for up to three samples ahead.

The liquid reagents for each enzyme chemistry are contained in cartridges that have compartments for the individual components. The components are combined when they are drawn precisely and sequentially into the barrel of the reagent dispensing syringe. At the right moment, the syringe dispenses the accurate volume of reagent into the cuvette. When the temperature of the reagent is stable, the dual ASTRA sample probes pick up the first serum sample on the sample tray. After the probes are rinsed, the transport moves to the enzyme modules, and the proper cuvettes are presented for injection of samples. Up to three injections occur for each patient sample per module. Carousel rotation places the correct cuvette beneath the sample probe and allows for mixing of a sample with reagent.

One serum sample is picked up every 80 seconds. Each 80-second cycle can be divided into two phases of the carousel: rotational and stationary. In the first rotational phase of the carousel, injection of sample #1 and reagent and intermediate absorbency readings for the sample occur. In the stationary

phase that completes this cycle, sample #1 begins a period of incubation, and reagent for sample #4 is loaded into the cuvette. In the second rotational phase of the carousel, sample #2 is injected and mixed, while the incubation of sample #1 continues. In the stationary phase of this cycle, sample #2 begins an incubation period, sample #1's chemistries are measured, and reagent for sample #5 is loaded into the cuvette. In the third rotational phase of the carousel, sample #3 is injected and mixed, while sample #2 remains in incubation. In the stationary phase of this cycle, sample #3 begins an incubation period, sample #2's chemistries are measured, reagent for sample #6 is loaded into the cuvette, and the used reaction mixture for sample #1 is discarded.

Ten absorbancy readings are taken in the 30-second measurement period. A regression line is calculated on these points, and the resulting slope (or A/minute) is used to calculate the final answer. The slope is checked for noise and nonlinearity, and there is an evaluation of out-of-range samples or substrate depletion. Samples determined to be out of range are automatically redone on a stat basis.

In late 1983, Beckman introduced the ASTRA IDEAL (Independent Discrete Expandable Analyzer for the Laboratory). The ASTRA IDEAL consists of two ASTRA 8 Analyzers joined by a central communications center called Link. Link is a Beckman-made Phoenix 8000 with 128 kilobytes of memory, which allows the operator to program and monitor the operation of the two ASTRA 8 Analyzers from a single keyboard and CRT (cathode ray terminal) display. As the tests are completed, Link collates and prints the results from both ASTRA systems on a single, patient-chartable report.

In addition to using Link to program the ASTRA IDEAL, the operator may use a graphics programming tablet. This tablet, which consists of an electronic slate and an attached electronic pen, allows the operator to program the ASTRA IDEAL directly from a laboratory requisition form, an innovation in chemistry analyzers. To program tests to the analyzers, the operator places the requisition form on the tablet and checks off the requested tests with the pen. The graphics tablet automatically recognizes the chemistries selected and transfers that information to the analyzers. Thus, the chance of error in transferring information from the requisition form is virtually eliminated.

As indicated previously, the success of ASTRA has primarily come from the software innovations which are not patentable--copyrighted, yes, patented no. While there are several patents applied for in the ASTRA hardware, none has been granted to date.

Recent Federal legislation to curb the growth in health care spending will greatly affect the procurement of ASTRAs and other laboratory analyzers. In the past, funds for the purchase, lease, or rental of laboratory equipment were fairly easy to come by. However, the Tax Equity and Fiscal Responsibility Act of 1982 (TEFRA) (Public Law 97-248) imposed maximum limits on the amounts of inpatient operating costs per case that will be reimbursed by Medicare for the services of doctors, hospitals, and laboratories. Furthermore, the Social Security Amendments of 1983 (Public Law 98-21) mandated the phasing in by Medicare of a prospective payment program for hospitals based on diagnosis-related groups (DRGs). The effect of Medicare's DRG hospital payment system is to take a now highly competitive marketplace and make it even more so. In order to stay competitive, therefore, a company must help the laboratory and hospital run more effectively and efficiently by

improving the laboratory's productivity, lowering the laboratory costs, and reducing the time of patient stay in the hospital.

The inventors, designers and marketers of ASTRA, its future replacement, and its competition must keep recent Federal legislation in mind as we are now in a highly cost-conscious marketplace. We and the hospital must continue our efforts to supply quality health care at a reasonable cost.

VIGNETTE #5
PNEUMATIC EXTRADURAL INTRACRANIAL PRESSURE MONITOR

Alan R. Kahn, M.D.
Consultant
Cincinnati, Ohio

INTRODUCTION

Intracranial pressure (ICP) is monitored to detect dangerous pressure increases in patients with head or spinal trauma, craniotomies, Reye's syndrome, and certain drug intoxications. Prior to the invention of the pneumatic extradural ICP monitor, monitoring of ICP was generally accomplished by means of fluid-filled catheters (or other similar appliances) with one end in direct contact with the patient's cerebrospinal fluid and the other end connected to a conventional pressure transducer. A device that detects ICP from a site outside the dura (the outermost and toughest membrane covering the brain) had been on the market for several years, but the pressure sensor in that device is very complicated and fragile, is slow to respond to changes, and is limited in accuracy. Thus, although that device established the usefulness of extradural ICP monitoring and has found application in certain medical centers, its use has been rather limited because of the complexity and inaccuracy of its sensing system.

The invention discussed in this essay is a new ICP monitoring system that allows extradural ICP measurement to be made simply, accurately, and at low cost. The invention includes a disposable sensor which is accurate, rugged, and very inexpensive to construct. The invention also includes a pneumatic system in a monitoring module which powers the sensor and provides self-checking and failure detection. The system has been designed as a sophisticated microprocessor-based instrument which was introduced to the market by Meadox Instruments, Inc.

THE INVENTION PROCESS

The ICP monitoring invention was not the result of new technological developments but was rather the application of a basic physical principle which had been overlooked in the area of pressure measurement. In recent years, advancements in technology have been made primarily in the field of electronics, and scientists and engineers tend to ignore other physical modalities such as pneumatics. Most of my inventions have been in the area of sensing and measurement and make use of basic physics rather than new technological developments. The necessary technical information can be found in any basic physics textbook.

I first had the idea for the basic technique for pressure measurement used in this instrument in 1964, as a way to measure the elasticity of human skin for a study on aging. At the time, I worked for a major corporation that did not see a market for a device with that application, and no product was ever developed.

In 1980, during a discussion on ICP monitoring, I realized that my old idea could be modified for use in this new application, providing significant benefits. I offered the company with which I was employed the opportunity to develop this product under a royalty arrangement, but the company declined. Subsequently, I left that company to join an existing research and development (R&D) consulting firm as an equal partner with the two existing partners, and we invested our time and personal funds to develop a prototype ICP monitoring system.

It took 6 months to build and test the first prototype in our laboratory and to perform preliminary tests in animals. Funding for these activities was provided by the three partners in our R&D consulting firm. A

510(k) report was submitted to the Food and Drug Administration (FDA), and FDA immediately responded with a set of written questions. I answered the questions, and the FDA allowed marketing of our product under the 510(k) "substantially equivalent" provisions of the Medical Device Amendments of 1976. To be found substantially equivalent to the extradural ICP monitoring device already on the market, our product did not have to be identical to that product but could not differ markedly in materials, design, or energy source.

The fact that the marketing of our device was allowed on a 510(k) submittal prior to the time we were seeking funding for made the process significantly easier. In this particular instance, therefore, FDA requirements perhaps were of some help.

FINANCING

Perhaps the most difficult step we encountered was in obtaining funding for design and marketing of the product. This was complicated by the fact that my partners and I were primarily interested in the R&D process and did not wish to get involved in marketing activities. Negotiations with a number of venture capital firms and other conventional sources of capital proved unsuccessful, because acceptance of the extradural method of ICP monitoring was limited by the existing product, and it was difficult to project just how an improved product would affect market growth. Therefore, very conservative sales projections were used in the business plan. These projections made the venture less attractive and affected our ability to obtain funding.

We finally established a joint venture with Meadox Medicals, Inc., an existing biomedical company that had facilities for manufacturing the sensors and saw our ICP monitoring device as an efficient way for the company to get into the area of electronic products. Each of the three partners in our R&D

firm ended up owning 9 percent of the new joint venture company and sharing a royalty on the product sales.

Our R&D company received a contract from the joint venture company to develop the product and subsequently to manufacture the electronic portion of the system until such time as the contractors learned more about the product and could take over all of the manufacturing.

PATENTS

Two patent applications covering our ICP monitoring product were submitted. The first one is about ready to issue, and almost all of the claims have been allowed. The patent was well written and the claims will probably be significant in allowing the company to recoup its investments and be profitable. Foreign patent applications have been submitted in several European countries covering both of the domestic patents. The patent proved important in obtaining financial support and also gave my two partners and me a tax advantage (royalties are taxed as capital gains rather than as ordinary income).

MARKETING

The existence of a market for an extradural ICP device was established by the sales performance of the less satisfactory monitoring device already on the market. Since it was difficult to predict how an improved instrument would affect market growth, the sales projections in our business plan were very conservative. Our market studies were essentially confirmed by those of the company that collaborated in the joint venture.

Meadox ICP monitoring systems are being marketed in the United States and Europe. Sales in the United States are proceeding as anticipated in our conservative projection. The depressed U.S. economy has hurt the sales growth of this product in two ways. First, it has reduced the purchasing power of hospitals from earlier projections and thus made sales more difficult. Second, the company marketing the product has received less revenues from its other product lines and has not been able to launch an effective marketing program for the ICP monitor. This second factor is probably the most important in causing the sales growth to proceed along the conservative path originally projected. Nevertheless, the venture is financially successful. European sales are beginning and are expected to represent about 30 to 40 percent of total sales in a few years.

Medicare and Medicaid programs do not directly affect the sales of this product. The electronic module is purchased as capital equipment by hospitals and the disposable sensors are charged through as patient charges. The Veterans Administration and Department of Defense are simply hospital customers, and their purchases provide no special advantages.

The market for the Meadox ICP monitoring system is not large and does not attract a large amount of competition. Growth in sales will come primarily from educating neurosurgeons about the advantages of extradural ICP

monitoring. Since the Meadox product is technologically advanced and provides numerous new features, it will not readily become obsolete and should enjoy at least a 5-year product life as originally projected.

VIGNETTE #6
INVENTION OF AN ELECTRONIC RETINOSCOPE

Aran Safir, M.D.
3 Ellsworth Avenue
Cambridge, Massachusetts

I was a teenager during World War II, and finished high school while still young enough to enter college before joining the military. Electrical engineering at Cornell wasn't what I had hoped for. Not only was there a total lack of non-technological studies in the engineering curriculum, but my classmates seemed to delight in the narrowness of that curriculum. To me, Engineering at Cornell seemed more like a trade school than a university.

I entered the U.S. Navy when I turned 18 and, on the basis of an aptitude test, I was placed in a training program for electronic technicians. The training was rigorous and thorough. It lasted for nearly a year and was better organized and taught than any other educational program I have ever been in.

My Navy training and World War II ended almost simultaneously, and I spent another year in the Navy working on aircraft radio and radar systems. During that year, I decided that medicine as a career might offer a good combination of science, technology, and the more social disciplines. I reentered college as a premedical student and, anticipating that I would probably spend the rest of my life immersed in the study of technological medicine, I fashioned a curriculum for myself that included the minimum scientific requirements for medical school and gave me a maximum opportunity to study literature. My major was English. Later I entered medical school. Medical school was not much fun; rote memorization is not my strongest skill. In retrospect, I can see the early indications of some factors that would later assume great importance in my life.

In high school, I had been seriously interested in photography, both the technology and the art. I had neither the time nor money for it in medical school, but I turned to optics to help me learn pathology. Each student was given sets of hundreds of slides of different pathological specimens to be studied under the microscope so that the features of various diseases could be memorized. While studying my slides, I discovered that I could place my microscope on the floor underneath a small table that had a ground glass top. When I darkened the room, I could see the projected image of the microscope slide on the tabletop.

I set about making my microscope into a projector. I bought a very powerful truck headlight bulb, attached it to a transformer through an adjustable resistor to operate the bulb well above its rated voltage, purchased some surplus lenses, and soldered together various rectangular and cylindrical tin cans to form a powerful substage lamp for my microscope. A small prism deflected the beam onto a white poster board on the wall, giving an image about 2 feet in diameter. With this device, several friends and I often studied our slides together and helped each other to learn.

Still, I thought of this as only a passing diversion, almost occupational therapy, because I had always been a good mechanic and enjoyed building things. About 2 years later, I had a brief exposure to ophthalmology, which is all that most medical students get. But even during that brief exposure, I realized that I had to make almost no effort to memorize those parts of the textbook that dealt with the formation of images by the eye. When we went to the ophthalmological clinics and could look into the eyes of patients through widely dilated pupils, I was thrilled by the magic of the eye as an optical instrument.

It was not until many months later, during my internship, that I had any opportunity to try my hand at surgery. When I found that I was good at surgery and enjoyed it, I began to think seriously of ophthalmology as a career. Still, it was my intention at the time to become a practitioner of ophthalmology and to return to my home town in order to establish a private practice. I had no real intention or desire to enter an academic career or to do research. I clearly recall that, at my residency interview at the New York Eye and Ear Infirmary, when the governing board of six senior surgeons asked me whether I intended to do research, my reply was, "I don't know. I think I would like to try, to see whether I'm any good at it."

I became a resident at the New York Eye and Ear Infirmary in 1956. That institution was known mostly for the excellent opportunity it gave the trainee to observe, learn, and participate in the practice of ophthalmology, but it offered little experience or opportunity in research. There was a small scientific program, but residents were rarely involved.

I reported for duty as a resident at the infirmary, on July 1, 1956, and, after being issued white uniforms, I was shown to the clinic. There I was put in the care of a second-year resident who was clearly too busy with his own clinical problems to spend much time with me He sat me down on a stool in a little booth where a patient sat next to a box of ophthalmological trial lenses. This was to be my first experience with refraction of the eye. Handing me a small instrument that resembled a flashlight, which he told me was a retinoscope, the second-year resident explained that I was to look through the little hole in the mirror and direct the beam of light into the patient's pupil. When I shined the light into the patient's eye, he explained, I would observe the patient's pupil glowing with light reflected from inside the eye. By tilting the mirror, I could make the reflected light

move across the pupil. I was to sit at arm's length from the patient and observe whether the light coming back out of the pupil moved in the same direction as the light I shined on the patient's face, or in the opposite direction. If the light moved in the same direction, I was to take lenses from one side of the box. If the light moved in a contrary direction, I was to take them from the other side of the box. I was to select lenses until I found those that made the light appear to stop moving. Wishing me good luck, the resident left me and went off to his own tasks.

I worked very hard at this first refraction and was quite upset by it. Like other young physicians, I had spent years learning to be competent in difficult matters. To be thrust suddenly back into complete incompetence and at the same time to have responsibility for patient care was disturbing to me. I recall going to lunch that day and sitting across the table from that same second-year resident. I told him, "If I can see those lights moving in the pupil, I'll bet I can make a photoelectric device that will see them better and faster." That was the conception of my idea of an automatic retinoscope.

During my residency, I was single and received room, board, uniforms, and $50 a month, my sole means of financial support, from the hospital. I had many evenings to read about retinoscopy (observing the retina to determine the state of refraction). The practice of retinoscopy requires considerable skill, but the principles of the technique are simple.

The retinoscope is basically a small lamp that shines light on a mirror with a hole in its center. Light reflected from the mirror enters the patient's pupil and illuminates the retina at the back of the eye. Nearly all the light is then absorbed, but a small fraction is reflected back, passes through the pupil, and leaves the patient's eye. The light that is reflected by the retina goes through the optical system of the patient's eye and acquires characteristics of that system.

The light rays leaving the eye can be either convergent, parallel, or divergent. If a patient's eye has excessive converging power, as it does in myopia (nearsightedness), the light rays leaving the eye will converge to a point in space at some distance in front of the eye. The distance from the patient's eye to that point is a measure of the amount of myopia (the closer the point to the eye, the greater the degree of myopia). An eye with no refractive error sends out parallel rays, and a farsighted eye sends out divergent rays.

The retinoscopist sits in front of the patient, looks through the sight hole in the center of the mirror, and decides whether the emerging light rays have reached a convergent point between him and the patient or have not converged by the time they get to his eye.

The rays coming from the patient's eye and meeting at convergent point form an inverted image of the retina. If the inverted image is formed in space between the patient and the examiner, the examiner can recognize the inversion; when he moves a light from right to left across the patient's retina, he sees the emergent light move from left to right in the inverted image. If the examiner places his own eye at a known distance from the patient's eye, he can then put lenses in front of the patient's eye that diverge or converge the light until the convergent point is brought to lie exactly at the position of the examiner's eye.

This is a crucial point, because on the patient's side of it, the image is not inverted, but a few millimeters away, on the examiner's side of it, the image is inverted, and the examiner can detect the sudden transition. By selecting the proper lenses, the examiner can bring this crucial point to lie at his own pupil, regardless of the patient's refractive error. The lenses required to do this are a measure of the patient's refractive state and supply

important information for other phases of the ophthalmological exam. It is through the lenses thus determined that the ophthalmologist can place images in good focus on the patient's retina and then test the patient's visual acuity.

Retinoscopy is the method that all refractionists use to measure the eye's optical characteristics objectively. The patient merely has to hold fairly still and gaze at a distant target. A skilled examiner can use retinoscopy to measure the refractive state of the eye of an infant, an anesthetized patient, or an experimental animal. Without an objective method of measurement, the doctor would have great difficulty in knowing how to proceed with the rest of vision testing. With the objective measurement, the examiner can go to the next phase, in which the patient's subjective responses are elicited, usually by the familiar technique of asking, "Which is better, one or two?" There is usually good agreement between retinoscopic measurements and the patient's subjective responses. Retinoscopy depends on the skill of the examiner, which varies considerably among practioners, and the patient's subjective responses are affected by personality and culture. The final judgment of how good the patient's visual acuity is and whether eyeglasses or other therapies are needed often requires a complex decision-making process.

I drew up plans for the construction of an electronic retinoscope and presented my ideas to the research committee of the New York Eye and Ear Infirmary. I asked them for sufficient laboratory space and a budget for some equipment so that I might try out my idea. They gave me about 6 feet of bench space in someone else's laboratory, allowed me to borrow a double-beam oscilloscope, and gave me a drawing account of about $500. I set to work building an instrument.

The hospital had a lathe and a drill press that were gathering dust, and they wanted to have a machine shop, so they asked me to build one for them. With the aid of one of the hospital's engineering staff, I constructed a machine shop to which I was subsequently given free access.

The chief administrator of the hospital recommended that I obtain a patent on my invention and suggested that I go to a former West Point classmate of his who had become a senior partner in a well-known New York patent firm. I did this, and the senior patent attorney assigned my case to a young patent attorney who had just joined the firm. That was when I found out that patent attorneys have degrees both in law and in a scientific discipline. In the young attorney's case, it was electrical engineering. The young attorney was also unmarried and had many evenings free.

The New York Eye and Ear Infirmary gave me a key to the library and research building, and over the course of about a year, with the aid of my attorney friend, I built a working model of the electronic retinoscope. The instrument was crude; the photocells were housed in the film carrier of an old Graflex camera, the image of the subject's eye was formed by a telescope made from the mailing tube that had held my diploma from medical school, and many of the parts were surplus that I had purchased at the outdoor hardware stalls on Canal Street in New York. By 18 months after I had started, I had a working model that demonstrated the feasibility of the method and was able to measure the refractive state of schematic eyes, which are metal and glass simulations of human eyes, commercially available to students of refraction who are learning retinoscopy.

An important scene stands out in my memory of those times. As soon as the retinoscope was operating satisfactorily, I invited a few close friends to come and see it. One evening we gathered in the lab: my patent attorney, my

girlfriend, and three of four ophthalmological buddies. I explained the device and what to look for on the oscilloscope, dimmed the room lights, and put the instrument through its paces. The outputs of the photocells could be easily seen on the oscilloscope. As the schematic eye was changed from nearsighted to farsighted, the oscilloscope tracing showed the change and clearly identified the crucial neutral point when the convergent point of the rays emerging from the eye was brought to precisely the correct distance, exactly as in clinical retinoscopy.

The instrument had a rotating light beam deflector for creating the scan of light across the eye. There were mirrors and lenses that cast moving patterns of light, not only on the schematic eye, but on the walls of the lab as well. The oscilloscope face flickered with bright green, evanescent tracings. In the darkened lab, it was dramatic.

As others became interested in the apparatus and began to operate it themselves, I stepped back to the far side of the room and watched them. A new feeling swept over me and I verbalized it internally: "Look at what I have done. What started as an idea in my head has created a new machine and has gathered these people here and captured their interest." I had a feeling of power and wonder, a very good feeling, and though I have experienced it again since then, it has never been so poignant. Surely, there are many reasons for people to experience such feelings, but invention is one that I have known, and I suspect that those who do not invent do not often appreciate the emotional importance of the act.

The young patent attorney was rather excited about this project because his review of the patents in existence had led him to conclude that we were opening up an entirely new field. The idea of dynamic scanning to measure an optical system had not been patented before. We filed a patent application in 1958 after about 2 years of effort.

Two important learning experiences began then for me; one with the U.S. Patent Office and the other with American industry.

Writing a patent application that has many claims, some of them quite broad, is a very difficult task. I had to teach my attorney a great deal about clinical optics and the practice of refraction. He then had to convert these ideas into legal language. This was a process requiring many interactions between the two of us, and it was costly. But it was necessary, for no company would discuss the invention with us until I had filed a patent application. At that time, many companies did not like to sign confidential disclosure agreements with inventors. They preferred, indeed insisted that patent applications be filed before discussions could begin.

When I had filed the application, and while I was beginning negotiations with optical companies in an attempt to interest them in the development of my invention, we got our first response from the U.S. Patent Office. The patent examiner in Washington wrote us a letter rejecting my patent application, citing former art as the reason for doing so. He sent us photocopies of the several patents that he felt anticipated my invention and therefore made my device unpatentable. When I read over the patents that the patent examiner sent us as evidence of my lack of invention, I was astonished, for none of the patents cited described a device that any reasonable person would consider to be the same as, or even similar to, my invention. Nevertheless, it became our task to draw up detailed written arguments and explain why my invention was different from those cited. Many months went by with no response from the Patent Office.

When the response came, it was another rejection, this time with another group of former patents cited as evidence against our case. This time the patents cited were more in the same ballpark as my invention, but again

there was no reasonable resemblance between my invention and those cited. Again, we drew up carefully worded and documented arguments to show that the patents cited were not relevant. Again, a long period of silence from the Patent Office ensued.

By now, I was no longer a resident of the New York Eye and Ear Infirmary. I had joined the faculty of the Albert Einstein College of Medicine in a half-time capacity in 1959 and had also established a private practice of ophthalmology in the other half time. At last, the third response came from the Patent Office. It was a terse letter stating that my patent application was once again rejected, and that this rejection would be final and irrevocable. A hearing on the matter would be held in Washington, and I might, if I wished, send my attorney to that hearing to argue.

In the meantime, I had decided that I needed further training and experience in vision physiology and the optics of the eye, and I had applied for and been granted a U.S. Public Health Service Postdoctoral Fellowship Award. I had gone to the Physiology Department of the University of Cambridge in England, spent a year there, and returned to the Albert Einstein College of Medicine.

I was earning little money then, in the neighborhood of $10,000 a year. To send an attorney to Washington, at $50 an hour, was formidable, but I decided to do it. When he returned from Washington, my attorney told me that at the hearing, when my case was called and he stood up and notified them that he had come to represent me, the presiding official said, "Patent granted." No arguments were made.

The time that elapsed from when I submitted my application to the U.S. Patent Office to when my the patent was granted in 1964 was 6 years. It seemed to me then that the U.S. Patent Office viewed its function as trying to

discourage me. The entire 6-year proceeding, which cost me a great deal of money and effort, seemed to be designed to test my persistence rather than my inventiveness. Recently, I have had dealings with the patent office, and have found them approachable and cooperative. Perhaps things have changed for the better.

During that 6 years, I tried to get a manufacturer interested in my invention. Although I had made a working model that demonstrated the feasibility of the idea, it was obvious that a clinical device that would refract eyes of living humans would require precision machining and optical techniques that I could never acquire in my own laboratory. There was no way that I could make this instrument without turning to an industrial company. Not until my patent application had been filed, were companies willing to talk with me.

I first approached the American Optical Co., one of the two largest ophthalmic optical manufacturers in the United States. I am almost embarrassed to state my reason for approaching them first. I had looked over the various retinoscopes that were sold in the United States and decided that I liked the design of the American Optical Co. the best. That was my sole reason.

After corresponding with me and reviewing my patent application, the American Optical Co. sent representatives to interview me and examine my working model. This was while I was still a resident. The company told me that my device was interesting, but that it would not fit into its corporate plans at that time. (The American Optical Company is now defunct.)

I then turned to the other large U.S. manufacturer of ophthalmic optics, the Bausch & Lomb Co. Again I exchanged correspondence and sent the company a copy of my patent application. Bausch & Lomb took a serious

interest in my instrument, and after sending their product manager for ophthalmic instruments and an engineer to visit me, remained interested. The product manager and his technical aids came to visit me a few times during my residency at the Infirmary. After several visits and months of deliberation, however, Bausch & Lomb informed me that it would take $100,000 to develop my instrument, and that the company was not prepared to spend that much money on the project.

My patent attorney then tried to interest other companies in the invention. We quickly exhausted the small number of companies that made ophthalmic instruments, and turned to other companies that made scientific instruments. None of these companies was sufficiently interested to send someone to see the device. They all rejected the idea out of hand, as not being within their realm of interest.

When I finished my 3-year residency in 1959, I had a patent application filed, a crude working device, and rejections from American Optical, Bausch & Lomb, and about a dozen more companies. So I got busy doing other things.

When I returned from England, I joined the Albert Einstein College of Medicine in a full-time position and was engaged in several other research projects. In 1964, my patent was granted. Because the New York Eye and Ear Infirmary had no patent policy, the patent belonged to me. If the infirmary had had the usual academic patent policy, claiming ownership of any invention made by any member of its staff using any of its facilities, this patent would never have been granted. When I left the infirmary in 1959, there were still 5 years of negotiations and many thousands of dollars that had to be invested in this project. I surely would not have done it if the patent were never to be mine, and I doubt very much that any administrator at the New York Eye and Ear Infirmary would have had either the knowledge or the desire to carry the

project forward. It was the prospect of ownership of my own invention that led me to go deeply into debt and to invest the large amounts of time that were required.

Now I must narrate a part of the story that is hearsay, for it was told to me by an official of Bausch & Lomb. Several years after the company had rejected my invention, it rearranged its Ophthalmic Instrument Division and appointed a new chief of research and development (R&D) of new instruments. The company decided that it had not had an important new product in quite a long time and that its reputation was beginning to slip because of this. Thus, Bausch & Lomb decided to develop an automatic electronic refracting device, gathered together a team of design engineers, and began the work.

It is common practice for industrial companies to arrange with the U.S. Patent Office to have all new patents that are issued within certain disciplines sent to them on a subscription basis, for a very small sum of money. When my patent issued in 1964, nearly 5 years after Bausch & Lomb had rejected it, Bausch & Lomb received a copy of it in the mail. When they went to the files and looked up the correspondence with me, they found that their design team had essentially redesigned an instrument that was clearly described in my patent. They had the choice of abandoning the project, with a financial loss whose magnitude I do not know, or of negotiating a contract with me. To go ahead with the project without a contract with me would have been legally indefensible.

One of the great surprises of my life was the letter that I received from Bausch & Lomb late in 1964, asking me if I was interested in licensing my patent to them. I was impressed; a young, unknown inventor was being approached by one of the largest and most prestigious optical companies, one of America's industrial leaders!

A contractual agreement was arranged between the Bausch & Lomb Co. and me. My new lawyer (I could no longer afford an expensive patent lawyer) told me that owners of patents never sell them outright, they usually grant a license to the manufacturer to make and sell the device. If the license is exclusive, granted only to that manufacturer and excluding all others, then any income to the inventor in the form of royalties is not taxed as ordinary income, but receives the special taxation treatment accorded to capital gains. Since the maximum tax on capital gains is significantly less than the graduated income tax on the same amount of income, it is very advantageous to grant an exclusive license. This preferential tax treatment is extended to inventors in order to encourage creativity.

Unfortunately, my lawyer did not build into our contract any mechanism that would punish the Bausch & Lomb Co. for slowness or inactivity in the development of my patent. This, as it turned out, was a serious error. The only clause in the contract that could act as a goad to the company was the standard clause that required the company to exercise "due diligence." To prove that a company has failed to exercise due diligence is extremely difficult and prohibitively expensive.

The company began work on the development of my invention, but didn't consult with me. I couldn't understand why there was so little communication between us. After many months had passed and I had no knowledge of what was going on with my invention, I was finally invited to come to Rochester, the company factory and headquarters, and meet with Bausch & Lomb's staff. I recall how excited I was by this trip. The taxi ride from the airport to the factory took me over the Bausch bridge to the huge, ancient, sprawling factory. Much of it reminded me of scenes from the Alec Guinness movie "The Man in the White Suit." Polished hardwood floors and varnished wainscotting on the walls were the decor of the executive offices.

Finally, the laboratory. There, in the center of a large and nearly empty room, sat my invention, the instrument that was going to do astonishing things. It would revolutionize refraction, allowing technicians to do work that had never been done before except by highly trained people at great cost in time. It would alter the patterns of health care delivery, making possible vision care in ways that had never been feasible before. I had dreams of doing wonderful, good things for society and making lots of money at the same time. But these dreams were never to be realized.

In the laboratory, I saw, for the first time, how Bausch & Lomb engineers had decided to translate my patent into three-dimensional reality. I had not been consulted at all about the design or construction of this instrument. Now this advanced working model was being used to refract a schematic eye, a glass replica of a human eye. In order to measure the refraction of the eye properly, the instrument had to start in one position, make its measurement, and then rotate a group of optical and electronic elements through 180 degrees. It was this necessity for rotation that had precipitated my invitation to Rochester.

The engineers and scientists told me that the instrument worked beautifully while it was refracting in the first position, but that it went "crazy" when rotation was started. This led them to conclude that the basic idea was probably defective because the rotation process would inherently make the measurements unstable. They showed me the instrument they had built, and we discussed the methods that they were using to align the instrument with the eye being measured. Within an hour, it became evident to me that they had made a fundamental error in their method of alignment. I knew exactly how to avoid the problems that they had encountered, because I had built an apparatus that had solved precisely that problem in my own laboratory where I was doing

physiological experiments that I had started in Cambridge. I advised them on how they should alter the apparatus in order to avoid the problems.

I was sobered by the knowledge that the engineering staff of this great optical company had fallen into an error that I, a clinician almost entirely self-taught in optics, was able to solve readily. My confidence in the expertise of Bausch & Lomb was seriously shaken by this experience. It was a warning of what was to follow.

After that incident, I was consulted more frequently and made more trips to Rochester, but almost invariably I was consulted after the Bausch & Lomb engineers had decided what to do, had done it, and had found that it didn't work well. I was called in as a "troubleshooter" and "problem solver." I was never asked to help them design in advance. I began to realize that I was experiencing what is know in industry as the "NIH syndrome," meaning "Not Invented Here." To this day, I am convinced that the Bausch & Lomb technical staff resented my involvement. One of the engineers who was very important to the project, in a moment of unguarded candor several years later, told me bluntly that he had invented the idea, but that I had managed to get to the Patent Office before him.

The gulf between the technical engineering staff and me might not have been so injurious if management had been effective. But it was in management that Bausch & Lomb was clearly at its worst. It took Bausch & Lomb 8 years to go from the time that we signed the contract until the company had an instrument ready to offer for sale. Considering that the life of a U.S. patent is 17 years and that a patent cannot be renewed, it is easy to understand how frustrated I became with this company while they consumed nearly 50 percent of the life of my patent through ineffectual management.

During that 8 years, Bausch & Lomb had four shakeups of management and appointed four different product managers for ophthalmic instruments. One of them told me in approximate terms what the company had spent already on this project, well before it was finished. The cost was astonishingly high. The projected sales price of the instrument rose higher and higher and eventually was more than three times what had been anticipated at the outset. So much money was spent on poorly managed R&D efforts that the company was unwilling to invest the amount necessary to create an adequate sales and field service force when the instrument finally did go on the market. I asked one of these product managers, after he had been in his new position for several months, what the status was of the project, one of his most costly projects, and he told me that he hadn't had the time to look at the product. He had never laid eyes on the instrument for which he had the responsibility of development and sales.

At one time, the project was nearly abandoned. I met with the product manager at an ophthalmological convention and, over lunch, he told me that the latest model of the instrument, which was now ready to refract human eyes, was doing the same sort of misbehaving that the early model had done with the schematic eye. Again he felt that the rotation of the instrument was inherently an impossible task, and he informed me that if the problem were not solved within 6 weeks the project would be abandoned irrevocably. On the way home from the convention, I thought this over and called the engineer in charge. I questioned him again about the technique of alignment, and again was able to determine the fundamental flaw in the alignment process that the people at Bausch & Lomb were now using. I advised him on how to correct this. When the correction was made, the alignment problem disappeared, and the project was not abandoned.

I know that these claims that I make to having saved the project from abandonment twice may sound self-serving, and I anticipate that the people at Bausch & Lomb may now view me with considerable hostility, but I no longer have any relationship with that company. The patent has expired, and even before it did, the company stopped making and selling the apparatus, and no longer even offers service on any of the machines that are in the field. There are not many machines out there, because the company never employed an adequate sales force. The people whom Bausch & Lomb selected to sell the instrument were not experienced refractionists or salespeople. Two men were taken from the company's Lens Manufacturing Division, taught how to operate the instrument, and sent to conventions to try to sell the instrument to clinicians. The instrument that they were asked to sell was not a truly finished product. The company spent so much money on the lengthy development effort, that it terminated it at the stage of the production prototype. The instrument that was sold was a replica of the production prototype which should have been further refined, going through one more stage of development before final marketing.

The Bausch & Lomb automatic retinoscope never achieved a significant share of the market. By the time Bausch & Lomb offered the instrument for sale, another company had already come out with an automatic refracting machine. Now there are nearly 20 automatic refracting machines on the market. Most of them are made in Japan, and one of them made by a major Japanese company uses the principle that I patented. To my astonishment, the Japanese company contacted me during the last year of the life of my patent, told me that the company had built an instrument that was based on my invention, and paid me royalties during the remaining year of the patent life. That was very honorable of the Japanese company, and it needn't have done that because I

would never have been able to sue the Japanese company if it had violated my patent rights. Lawsuits concerning patent violations are unbelievably expensive, and only inventions that are creating large amounts of income result in lawsuits.

I made very little money from this invention. If I were to reckon my income from it in dollars earned per hours spent, I would have been far better off to have spent my time practicing ophthalmology.

VIGNETTE #7
THE PERCEPTION OF NECESSITY AND THE INVENTIVE PROCESS: THE STERNAL APPROXIMATOR AND PERCUTANEOUS INTRA-AORTIC BALLOON CATHETER

Sidney Wolvek
Director of Advanced Research for
Disposable Products
Datascope Corporation
Oakland, New Jersey

INTRODUCTION

Three hundred years ago, writing on innovations, Sir Francis Bacon stated:

> It is good also not to try experiments in states, except the necessity be urgent, or the utility evident; and well to beware that it be the reformation that draweth on the change and not the desire of change that pretendeth the reformation.

It has often been said, and rightly so, that necessity is the mother of invention. However, it is the perception of necessity that may truly be called the father of invention, the progenitor of the inventive process. Thus, the making of an invention is normally comprised of two elements--the perception of a need or problem and the devising of a solution. There are many examples of instances in which the identification of the problem has been the major stumbling block. The literature is full of examples of inventions that were made quite rapidly once the problem to be solved had been correctly diagnosed. Of course, there are also many examples of inventions that were years in the making following the identification of the problem.

In this essay, I will discuss two medical innovations--the sternal approximator/suture locking system and the percutaneous intra-aortic balloon catheter--each responding to a need. The percutaneous intra-aortic balloon responded to a real need that had been recognized for some time in the literature and in patent specifications. The sternal approximator/suture

locking system responded to an equally real but only dimly perceived need. The percutaneous intra-aortic balloon was developed by an inventing team supported by corporate funds and operating within the guidelines set forth in the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act. The sternal approximator was invented by a lone inventor supported by private funds in the years prior to 1976. Both inventions have become state-of-the-art.

STERNAL APPROXIMATOR/SUTURE LOCKING SYSTEM

In April of 1971, while working as a consultant in assisted circulation, I became interested in developing methods and means that might extend patient time on the heart-lung machine, thus permitting longer and more complex open-heart surgery. The heart-lung machine is the device that makes open-heart surgery possible--by taking over the oxygenation and the pumping of the blood through a patient's body, it allows a surgeon to operate in the patient's empty, nonbeating heart.

I approached an old friend, who was a cardiac surgeon, with my thoughts. He agreed that the problem was worth investigating and invited me to observe his next open-heart procedure so that I might better understand the details of heart-lung machine function.

The procedure I observed was an aortic valve replacement. In addition to requiring support of the patient on cardiopulmonary bypass, this procedure required extremely precise and sophisticated operative techniques. Such techniques were much what I had expected, having previously observed some thoracic surgery in my work on assisted circulation.

The technique used to join the halves of the split sternum (breast bone), however, was a great surprise to me. At the outset of the operation, the surgeon had to split the sternum lengthwise to provide access to the heart and the ascending aorta. In order to reunite the flat bone--a process called "sternal approximation"--six stainless-steel monofilament suture wires swedged to chisel-pointed needles were passed by the surgeon through both halves of the patient's sternum. Then, using sterile automobile pliers, the surgeon twisted these suture wires until the loops were tight and the halves of the sternum were brought together. The twisted wire pigtails were cut off about 2 cm from the breast bone, and the remaining pigtails were then pushed down into the wound so that they lay along the sternal split. Finally, the subcutaneous tissue and skin incisions were sutured closed over the line of sternal wire sutures.

After the operation, I expressed my surprise to the surgeon about what I considered to be a rather crude method of sternal approximation, especially after the exquisite work that had been done within the chest. I asked if there might not be some better way, and he replied, "That's the way we've always done it. It works." In later operating room observations and conversations with him and with other cardiac surgeons, I learned that although twisted wires had become the accepted method for approximating the sternum, the method presented many serious problems:

- The suture wires were often overtwisted and fatigued so that they broke during the procedure or immediately afterwards, necessitating a return trip to the operating room.
- The twisted wires sometimes became untwisted, again requiring a return trip to the operating room.

- Insufficient tightening of the twisted wire loops or loosening as a result of patient movement or coughing allowed the split edges of the sternum to grate against each other, resulting in pain and slow healing at best and in sternal dehiscence and infection at worst.
- The twisted pigtail ends of the suture wires sometimes pressed against the surface of the sternum, causing postoperative pain.
- Often, the sharp ends of the twisted pigtails would not lie flat and could penetrate the skin of the chest, creating an immediate infection path into the thorax.
- The wire pigtails often caused an unsightly scar.

From my observations and discussions, I decided that the problems being encountered could best be solved by devising a better means of sternal approximation. It seemed to me that the medical community was concentrating on minimizing the adverse consequences of the accepted technique rather than on devising a new technique entirely. I concluded, however, that no matter how skilled the surgeon, the drawbacks of the existing method could never be fully overcome; therefore, a new approach was called for. When I asked my friend if he would try a new method of sternal approximation if I could develop one, he replied, "Yes, if you can convince me that it is safe and effective."

Having concluded that an entirely new approach was called for, I decided that my first step would be a careful analysis of the existing method of sternal approximation, identifying both its strong points and its problems, and identifying the source of each problem. As far as I could see, only a few aspects of the existing method were acceptable. The steel-suture-wire/bone-penetrating-needle combination, the low carbon 300 series stainless steel of which they were made, and the actual placement of the suture wires through or

around the sternum were all satisfactory and did not contribute to the method's shortcomings.

Assuming that the new method would incorporate the present suture wire and involve no new method of suture placement, I determined that the new method would have to:

- o employ the same no. 5 stainless steel suture wires which were currently in use,
- o apply a controllable tension to the wires in order to eliminate overtensioning, undertensioning, or fatiguing the wires,
- o lock the tension suture wires in a secure method that would not permit slippage nor incur breakage,
- o eliminate any short wire ends that might puncture the patient's skin or dig into the surface of the sternum,
- o permit usage by surgeons trained in the state-of-the-art technique without undue deviation from the state-of-the-art,
- o be simple to use without adding to the operating time, and
- o not contribute to scarring.

My study of the situation led me to believe that in order to be able to control the tensioning of the suture wires in the new method, the wire tensioning operation would have to be separate from the wire locking operation. I also decided that a locking method that avoided twisting the wires would require a new mechanism. If the mechanism were metallic, it would have to be made of exactly the same type of stainless steel as the suture wires in order to avoid any electrolytic action after implantation. So as not to contribute to undue scarring and not to cast a large radiopaque shadow that might inhibit postoperative X-ray evaluation of the patient, the mechanism would also have to be small.

The first element of the invention I designed was a caliper-shaped device, the two legs of which could be moved apart from each other by means of a rack and pinion arrangement. A locking mechanism at the end of each of the legs allowed rapid insertion of the opposed ends of the suture wire. Cams locked the wire in place automatically as tension was applied. A knob-like handle rotated the pinion gear, which was capable of applying a great deal of linear force to the long gear rack which separated the legs of the device, thereby applying tension to the ends of the suture wire which were locked into place on the legs. The wires were, of course, the exact no. 5 stainless steel suture wires which were then in use.

The second element I designed, to eliminate the need for twisting the suture wires pigtail fashion, was a small, rectangular suture locking plate. The plate had two holes drilled parallel to the long axis and to each other, was approximately 3 x 2 x 1.5 mm in size, and was milled from stainless steel of the same composition as the suture wires. Like the suture wires, the plate was in an annealed or nonhardened state.

The third element of the invention consisted of a plier-like device fitted with crimping jaws of hardened steel. The box joint of this crimping instrument was capable of providing a considerable pressure to the crimping jaws. The closed distance between the jaws could be regulated by means of a stop-screw, which was then locked in place.

The early development of this invention was limited more by lack of funds than by technical problems. At this stage, I was working alone with extremely limited resources. The resources had been provided by my brother-in-law, who had great faith in me and in the new invention. In order to conserve expenditures, my first feasibility prototype incorporated a rack taken from a wrecked typewriter and a pinion that had once been part of a

World Was II fighter plane. A local machine shop constructed the tensioner and the crimping pliers from my sketches. A friend allowed me to use his milling machine to shape and drill the holes through the locking plates.

The distance between the holes and the distance between the holes and plate edges, I thought, would be critical in making an effective suture lock that would neither allow stretching of the loop nor cause weakening of the suture wire beneath the crimp. To perform in vitro feasibility testing of the geometry of the various elements and ease of use, I used cow's ribs purchased from a local butcher and split on a band saw. The Academy of Aeronautics at La Guardia Airport, which is my alma mater (1941), kindly allowed me to use its Instron tension-testing maching to test and record the tension of the loops employing various locking plate geometries. (I am pleased to say that several years later in a favorable article describing his clinical experience with the Wolvek approximator (Annals of Thoracic Surgery, November 1978), Dr. William S. Stoney of the Vanderbuilt University Medical Center in Nashville almost duplicated my in vitro test figures.)

At the end of October 1971, 6 months after I began working on the problem, clinical prototypes of all three elements of the invention had been tested and evaluated in the laboratory to the point that I felt it was ready for clinical trials. The surgeon in whose operating room I had first observed sternal closure problems had been kept apprised of my progress and had regularly given me his reaction to advancements and evaluations. He too felt secure about testing my invention clinically. It should be remembered that the Medical Device Amendments to the Food, Drug, and Cosmetics Law were not enacted until 1976. Even without constraints and implications of a protective law, however, no responsible researcher would try a new medical device on a patient--no matter how great the potential benefit to the medical community

and, of course, to the patient--without first being satisfied that the device had been carefully built and thoroughly tested.

The first clinical use of the sternal approximator/suture locking system took place on November 9, 1971, in the open-heart operating room of the Jersey City Medical Center. Prior to sterilization, a suture locking plate was placed on each of five suture wires, and the extreme end of each wire was bent over to retain the plate. (The plate could not slip off the other end of the wire because of the presence of the needle.) Following sterilization, the sterile wires were placed through the sternum in the standard manner. When all five sutures had been placed, the needles were cut off with a sterile wire cutter and discarded. The newly available end of each wire was then passed through the unoccupied hole in the plate from the opposite direction so that the ends of the newly formed wire loop crossed each other within the plate. Both ends of the uppermost wire--the one closest to the patient's head--were then placed into the cams on the legs of the tensioning instrument, and the operating knob was rotated by the surgeon. The approximator legs moved apart from each other, thereby closing the wire loop which passed through both halves of the sternum and through the parallel holes of the locking plate. The split edges of the sternum could be seen approaching and finally abutting to close the sternotomy. At this point, the crimping plier was placed over the locking plate and the plier closed until restrained by the stop screw. The procedure was repeated for each of the five sutures, and the ends of the wires were then cut off at the point they exited from the locking plate.

The sternal closure system had performed easily and without incident. On the basis of this trial, I decided to make the plate a little longer since the extremely small plate had not quite straddled the operative groove in the periosteum (connective tissue covering the bone). This had made crimping a bit clumsy.

The second clinical use of the sternal closure system was at the Cornell-NY Medical Center. Once again, the system was employed effectively, and a modification to the crimping jaws suggested itself. Successful clinical use of the system continued in hospitals such as Massachusetts General, Sick Children's Hospital in Boston, Mt. Sinai in New York, Deaconess Hospital in Boston, the Cleveland Clinic, and Johns Hopkins Medical Center in Baltimore. A U.S. patent application was filed and the patent was issued on April 9, 1974.

The immediate recognition of the advantages of the early prototype of the new system made the decision to proceed beyond the prototype stage apparent. In May of 1973, The Annals of Thoracic Surgery published an article entitled "A New Method of Sternal Approximation" by Dr. J. Timmes and colleagues. The Association of Operating Room Nurses reprinted this article in the December issue of its journal.

The question that remained was the method of commercialization. The total market for the disposable elements of the invention--the suture locking plates--at least in the United States, was easily estimated simply by multiplying the number of open-heart procedures done in the previous year by an estimated growth factor and by multiplying that number by five (the number of sutures per procedure). The total potential market for the nondisposable elements--the sternal approximator and the crimper--was estimated by multiplying the number of open-heart operating rooms in the country by a maximum of two. I quickly recognized that the major revenue to be derived from the invention would be from the sales of the suture locking plates. Although the number of potential sales looked attractive, however it could not justify our going into the surgical device manufacturing business.

Rather than going into the surgical device manufacturing business ourselves, therefore, we decided to look for a manufacturing company that enjoyed a good reputation in the medical community in order to enter into a licensing arrangement with them. Eventually, we negotiated a licensing agreement with the Pilling Co. The actual royalty percentage hinged upon the issuance of a patent.

Although it has been argued that the actual value of a patent in protecting an invention is proportional only to the amount of funds that the patent holder has available for litigation, the real value of a patent to an independent inventor lies in enabling the inventor to enter into negotiations and to make a more profitable agreement with a commercializer. It would be very difficult to disclose proprietary information to a potential licensee without having at least a patent application number on which to lean for protection. Since the patent process currently takes from 1 to 2 years, many licensing discussions are initiated under the protection of a patent pending serial number, as was the sternal approximator/suture locking system.

Earlier in this essay I mentioned that the sternal approximator was conceived, developed, and commercialized some years before the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetics Act. I have also sought to point out that each early clinical use of the device was performed by an esteemed cardiac surgeon in a university-affiliated hospital. In its insistence on responsible research to ensure the safety and efficacy of medical devices, the 1976 medical device law cannot be faulted. It is important to realize, however, that the additional commitment of resources that the act requires must have an inhibiting, if not an actually stultifying, effect on the individual inventor working with limited funds. I do not mean to say that the 1976 act would have prevented the development of the sternal

approximator. However, had the act been in existence when the sternal approximator was being developed, it is extremely doubtful that the development of this invention would have produced as expediently as it did.

PERCUTANEOUS INTRA-AORTIC BALLOON CATHETER

Whereas the need for a new method of sternal approximation was only dimly perceived at the time I began my work, the need for a more easily insertable intra-aortic balloon had long been apparent. By 1978, intra-aortic balloon pumping was being applied to patients suffering from failure of the left ventricle of the heart due to a wide variety of causes, and intra-aortic balloons were being manufactured in a number of different sizes and designs. The science of intra-aortic balloon pumping had come a long way in its first decade, but the method of inserting the balloon had not progressed.

An intra-aortic balloon is a device which, for a limited period of time, augments the natural pumping action of the heart. The benefits derived from use of intra-aortic balloon pumping are many, two of the most important being increased blood supply to the coronary artery of the ischemic heart muscle and lowered workload and oxygen demand of the damaged myocardium.

The surgically insertable balloon that had become state-of-the-art in 1978 consisted of a sausage-shaped balloon roughly 24 cm long by 16 mm in diameter attached over one end of a catheter tube. Most commonly, this device is fed into the patient's femoral artery in the groin and is then guided through the arterial system until the balloon chamber is in the aorta-(the primary artery leading from the heart). Once properly positioned in the aorta, at a point just short of the entrance of the subclavian artery into the aortic arch, the balloon is repeatedly inflated and deflated in rhythm with the patient's heart. A series of holes in the catheter tube within the

balloon allows a gas (e.g., carbon dioxide or helium) to inflate and deflate the balloon very rapidly in rhythm with the heart's cycle.

The actual pumping and removal of the gas is performed by a console which electronically translates the patient's cardiac cycle (the patient's electrocardiogram or aortic pressure curve) into triggering signals that initiate balloon inflation and deflation. During the systole portion of the patient's cardiac cycle (when the left ventricle is ejecting blood into the aorta in order to perfuse the body), the console causes the balloon to deflate. The deflation of the balloon creates a partial vacuum within the portion of the thoracic aorta that the balloon occupies, thus lowering the systolic aortic blood pressure. The ventricle of the heart is then able to eject its charge of blood more easily into this region of lowered back pressure. The workload on the patient's heart is thereby reduced, as is the heart's need for oxygen.

At the diastole end of the cardiac cycle (while the ventricle is refilling), the console causes the balloon to inflate. The rapidly inflating balloon forces the blood within the aorta backwards toward the patient's heart and brain and forward toward the kidneys and the rest of the body. This enables a marked increase in the blood flow, particularly to the coronary arteries which supply blood to the heart muscle during diastole. Since the intra-aortic balloon is in its pumping phase while the heart is relaxed and is relaxed when the heart is pumping, Dr. Adrian Kantrowitz (generally credited with having developed and perfected this therapy) called the action of the intra-aortic balloon pump "phase-shift pumping." Dr. Kantrowitz's early cases were with medically treated patients suffering from irreversible shock secondary to myocardial infarction (heart attack).

In 1978, the surgical technique for inserting the balloon normally required assembling a vascular team and readying an operating room before any work could be done on the patient. The surgery itself involved making an incision down to the femoral artery, opening the femoral artery and attaching a vascular graft, and then feeding the balloon into the artery. It was not uncommon for the entire procedure (including the assembly of a surgical team) to take 2 to 3 hours, and seldom could the procedure be accomplished in less than 45 minutes.

The need for reducing the time it took to initiate pumping was perhaps brought into sharpest focus by the statistics of the literature indicating a direct relationship between patient death and the amount of time that the patient remained in cardiogenic shock prior to the initiation of intra-aortic balloon pumping.

Another problem was that because of the complexity, time requirements, and the attendant risks of the required surgical insertion, many patients were unable to undergo the procedure. In addition, since the standard insertion technique necessitated feeding the balloon from the groin through the patient's arterial system to the aorta, the limitations imposed by tortuous or diseased femoral/iliac arteries often prevented insertion and advancement of the relatively bulky intra-aortic balloon through the limited opening into the artery (the arteriotomy) and into the thoracic aorta. To make intra-aortic balloon pumping available to the large patient population still being denied its advantages, an improved balloon and an easier method for its insertion were called for.

I had had the good fortune to have worked with Dr. Kantrowitz during the early years of intra-aortic balloon development, prior to my work as an independent inventor. In 1976, I was employed by Datascope Corp., a leading

manufacturer of intra-aortic balloons and balloon pumping consoles, as chief development engineer for disposable products. Bruce Hanson, then manager of research and development, was my immediate superior at Datascope, and the two of us generally worked together as an inventing team, discussing the shortcomings of existing devices and the needs of the marketplace and then attempting to satisfy those needs by solving the problems we saw.

One of the most successful and rewarding projects to which Bruce Hanson and I directed our energies involved designing and fabricating a more easily insertable intra-aortic balloon which would overcome the most serious drawbacks of the existing balloons and make balloon therapy available to many more patients. The design, fabrication, and testing of countless prototypes and variations necessarily occupied most of our time in this effort. During our consideration of one of these prototypes, we came to realize that if one end of the balloon were allowed to rotate freely in relation to the other end, which would remain fixed to its catheter, the balloon could be twisted on its own longitudinal axis to a diameter that was smaller than that of its catheter. The implications of this discovery were so exciting that our major effort was directed toward developing this new concept.

Since we wanted the twisted diameter of the balloon to be no larger than that of the catheter tube, the catheter for the new balloon could no longer be extended through the length of the balloon chamber. Therefore, we substituted an extremely slender wire-like member to support the twisted balloon and keep it from folding back upon itself and also to provide the stiffness needed to insert the balloon into an artery and feed it up into the aorta. Many prototypes were tried in our all-out effort to perfect manufacturing techniques and minimize costs without sacrificing any of the product's advantageous features.

The new balloon was developed to the point where its greatest diameter, when twisted for insertion, was that of its catheter tube--12 French. The diameter of the wrapped balloon portion had been reduced to less than that of the tube itself--a design feature which permitted insertion of the balloon "percutaneously," that is, through the skin. Not only did our invention simplify insertion of the balloon, but it eliminated entirely the need for the surgery!

The small catheters required for cardiac angiography had been inserted percutaneously for some time, via the Seldinger technique. This technique involves inserting a needle into the artery through the skin, then inserting a soft guide wire through the needle into the artery and removing the needle. To stretch the needle puncture, a dilator together with a thin-walled sheath is fed over the guide wire into the artery. When the guide wire and the dilator are removed, only the soda-straw-like sheath is left, partially in the artery and partially outside of the body. The small angiographic catheter is then easily inserted into the artery through the sheath.

Until the introduction of our percutaneous intra-aortic balloon, this technique had been limited to the insertion of relatively small catheters, those with sheaths smaller than 7 French. It occurred to us, however, that there was nothing sacrosanct about the small-sized catheter. If we could use a 12.5 French sheath, we reasoned, we could eliminate surgery entirely. We undertook a series of animal experiments, which proved that the percutaneous insertion of an introducer sheath that allowed passage of a 12 French balloon catheter was safe and effective and that the puncture wound in the artery closed spontaneously upon balloon removal. The experimental series, of course, was also designed to provide safety and efficacy data.

In February of 1979, the first clinical percutaneous insertion of an intra-aortic balloon was performed with complete success. The total time required from femoral puncture to the initiation of pumping was 12 minutes. Since then, the Datascope percutaneous intra-aortic balloon, which has been given the trademark PERCOR \, has been used in many thousands of patients and has saved countless lives.

The new invention has made intra-aortic balloon pumping available to a greater number of patients in a greater number of hospitals, usually within minutes of determining the indication for pumping. The 2 or 3 hours that had been required to assemble a vascular surgical team, to schedule an operating room, and to perform the surgery have been eliminated. A cardiologist with standard angiography skills and equipment can now perform the percutaneous insertion procedure in under 5 minutes and without the presence of a surgeon. The control of bleeding after balloon removal is achieved simply by the application of manual pressure to the puncture site. The percutaneous procedure also allows the prophylactic insertion of an intra-aortic balloon prior to coronary angiography or anesthesia induction in selected high-risk patients. Finally, the new invention has made intra-aortic balloon pumping available to a large number of patients in whom the stiffer, bulkier, surgical balloon could not be inserted because of tortuous arteries or vascular disease. Its extreme flexibility enables it to navigate tortuous arteries readily.

Despite the success of Datascope's PERCOR \ balloon and the great step forward which it represented, our work in this area was far from over. We have made numerous additional improvements. None of them, however, has been as important or as dramatic as the original breakthrough upon which the basic percutaneous balloon was based. Our original concept remains the cornerstone about which all the improvements are built.

Several months after the introduction of percutaneous intra-aortic balloon pumping to the medical community, we examined the needs that clinical experience in the new discipline was making apparent. One need was the ability to monitor aortic pressure so as to facilitate the timing of balloon inflation. In addition, many physicians had requested a percutaneous intra-aortic balloon which could be inserted over a guide wire in cases of extreme arterial tortuosity.

In answer to these needs, Bruce Hanson and I developed a dual-lumen balloon which was percutaneously insertable. Commercial distribution of the dual-lumen percutaneous balloon began in September 1981. In the dual-lumen balloon, the wire rod (the stylet) runs through a very narrow soft polyurethene central tube (lumen) and is anchored to a wrapping knob outside of the body. The wrapping system makes it easier for a physician to wrap the balloon consistently and uniformly each time a balloon is prepared for insertion. It also presets the correct number of turns needed to wrap the balloon, thereby preventing overwrapping, and ensures that unwrapping will be accomplished automatically with the same number of turns. The wrapping stylet may be left in the balloon if the standard percutaneous insertion technique is to be used, or it may be removed from the balloon so that the balloon may be inserted over a soft tip safety guide wire. The extreme softness and flexibility of the balloon's inner lumen permit the balloon to follow the safety guide over an extremely tortuous arterial pathway and to avoid the possibility of arterial penetration by the balloon tip.

In addition to allowing insertion over a safety guide, the central lumen of the balloon provides the physician with the opportunity to monitor arterial pressure when radial artery pressure is not available. It may also be used for the hand injection of radiopaque contrast material to determine the balloon's position, or it may be used for arterial blood sampling.

Because of Datascope's long experience in the manufacture of intra-aortic balloons, our interactions with the Food and Drug Administration prior to commercialization of the new percutaneous balloons went smoothly and without complication.

Patents for the balloons were applied for and were issued. A patent cannot prevent infringement, but it does allow a legal response to infringement. Therefore, the patentability of a new invention or innovation and the defensibility of a resultant patent always forms a major consideration in the decision to commit corporate resources to a new project.

In contradistinction to an independent inventor working with limited funds, the corporate inventor or inventing team working with internal corporate funds is not constrained by the need to obtain adequate funding. The inventive effort can therefore be placed where it belongs--on the invention rather than on raising the money necessary to back the invention's development.

It is quite possible that the extreme sophistication of today's science and the exponential rate of growth of modern knowledge has outpaced the resources of the individual inventor. Perhaps the new medical inventions and innovations will be limited to those of the corporate or university inventing teams. Whatever the case, invention and innovation will always require the recognition of a need and the creativity to satisfy the need.

VIGNETTE #8

THE FIRST SUCCESSFUL IMPLANTABLE CARDIAC PACEMAKER

Wilson Greatbatch
President
Greatbatch Enterprises, Inc.
Clarence, New York

On April 7, 1958, Dr. William C. Chardack, Dr. Andrew Gage, and I implanted the first self-powered implantable cardiac pacemaker in an experimental animal. In October of that year, Dr. Ake Senning in Stockholm attempted the first human implant. That device worked only 3 hours and then failed. A replacement device worked 8 days, after which the patient survived unstimulated for some 3 years. Two years later, in 1960, our group accomplished the first successful implant of a cardiac pacemaker in a human being.

At the time, we optimistically predicted an annual usage of perhaps 10,000 pacemakers per year. Remarkably soon thereafter, the implantable pacemaker became the treatment of choice for complete heart block (impairment of heart exitation) with Stokes Adams syndrome. Today, 25 years later, pacemakers have assumed forms and functions that we never dreamed of, and the world pacemaker market is well over 300,000 units per year.

Electricity and electronics always fascinated me, perhaps because of their mystery. Something was happening that you couldn't see, or feel, or hear. You needed a meter or an oscilloscope or at least a neon bulb to detect it, and then you had to interpret what the reading meant. I know I was thoroughly hooked early in my teens when I built my first two-tube short-wave receiver and listened to London, England, on a coil I had wound myself. I think I was 16 when I passed the test for my radio amateur's license. I was

also very active in Boy Scouts and joined the Sea Scout Radio Division which had a station at the Buffalo, New York, Sea Scout base next to the New York State Naval Militia in Buffalo.

In 1939-1940, some of us joined the Naval Reserve unit next door. The fact that we had amateur radio licenses qualified us for a noncommissioned officer's rating. My time in the Navy was spent repairing electronic equipment on a destroyer tender, "pounding brass" as a navy radio operator on merchant ships in convoy to Iceland, teaching in a Navy radar school, and finally flying in combat in dive bombers and torpedo bombers as a rear gunner off an aircraft carrier (the Monterey; former President Ford was our deck officer). Our nine-plane squadron used up 27 airplanes in 6 months of combat. A third of our crew was killed.

With World War II was over in 1945, I returned to Buffalo with my new bride Eleanor, worked a year as an installer-repairman with the New York Telephone Co., and then decided to register in the School of Electrical Engineering at Cornell University in Ithaca, New York. At first, Cornell would not admit me. So I went out to Danby, 6 miles south of Ithaca, and bought a farm. Then I came back and presented myself as a "resident student" and got in.

Cornell has always stressed breadth of background. As students, we got enough math to qualify as high-school math teachers and more physics and chemistry than most other schools ever provide. Most of my work since my undergraduate days at Cornell has been outside my specific training as an electronic circuit designer. The background I got at Cornell has enabled me to branch out when necessary into nuclear physics, electrochemical polarization of physiological electrodes, battery chemistry, the physics of welding, and the countless other things I have had to do in the past two decades to keep our corporate heads above water.

As an undergraduate at Cornell, I got my first exposure to medical electronics. I was a GI bill student, my only honor being that I had more children--three at the time--than anyone else in the class. To feed my family, I had to double my GI bill income. During one period, I ran the university AM/FM transmitter on weekends. At other times, I worked as an electronics technician, building intermediate-frequency amplifiers for what was later to become the Arecibo, Puerto Rico, radiotelescope.

One day in an adjacent lab, I saw a Cornell graduate student, Frank Noble, measuring the blood pressure in a rat by measuring the change in tail size as a pulse of blood traversed it. His electronic plethysmograph was part of the instrumentation at the psychology department's Animal Behavior Farm at Varna, New York, near Ithaca, under Dr. Urner Liddel. Dr. Liddel's experiments at the Animal Behavior Farm dealt with conditioned reflex under neurosis, and Frank was responsible for instrumenting some 100 sheep and goats for heart rate, blood pressure, etc. I became intensely interested, and when Frank left to become head of an electronics laboratory at the National Institutes of Health, I inherited his job.

During the summer of 1951, a couple of New England brain surgeons spent their summer sabbatical at the farm, doing experimental brain surgery on the hypothalamus of the goats. The surgeons carried their lunches in brown bags as did I, and we would sit on the grass in the bright Ithaca sun at noontimes and talk shop. During our conversations, I learned much practical physiology. One day, the subject of heart block came up. Heart block is the impairment of conduction in heart excitation. When the surgeons described it, I knew I could fix it, but not with the vacuum tubes and storage batteries we had then.

I went on into aerospace work at Cornell Aeronautical Laboratory in Buffalo, keeping all this in my mind and not knowing that Paul Zoll at that time was building his first external cardiac pacemakers in Boston.

In 1953, we saw our first transistors, and I built some amplifiers with them. By the time the first really commercial silicon transistors became available (at $90 each!) in 1956, I had become an assistant professor of electrical engineering at the University of Buffalo. I was also spending some time with Dr. Simon Rodbard and Dr. Robert Cohn at the old Chronic Disease Research Institute in Buffalo.

Sy Rodbard was interested in fast heart sounds, which we recorded off an oscilloscope with a movie camera. I wanted a 1 Khz marker oscillator and built one out of a single transistor and a UTC DOT-1 transformer. My marker oscillator used a 10K basebias resistor. One day, I reached into my resistor box to get a 10K resistor, but misread the colors and got a brown-black-green (1 megohm) instead of a brown-black-orange resistor. The circuit started to "squeg" with a 1.8 ms pulse followed by a 1-second quiescent interval. During the quiescent interval, the transistor was cut off and drew practically no current. I stared at the thing in disbelief and then realized that this was <u>exactly</u> what was needed to drive a heart. I built a few more. For the next 5 years, most of the world's pacemakers were to use a blocking oscillator with a UTC DOT-1 transformer just because I grabbed the wrong resistor!

I found little enthusiasm locally for an implantable cardiac pacemaker. Sy Rodbard and Bob Cohn were not much interested in pacemakers, although both were cardiologists; nor was Dr. Dave Green, a cardiologist at Buffalo General Hospital. So I kept on looking. Each medical group I approached said, "Fine idea, but most of these patients die in a year or so. Why don't you work on <u>my</u> project?"

Then one day in the spring of 1958, I visited Dr. William Chardack, chief of surgery at the Veteran's Administration (VA) Hospital in Buffalo. It was after that that things began to happen.

In Buffalo, we had the first local chapter in the world of the Institute of Radio Engineers, Professional Group in Medical Electronics (the IRE/PGME, now the Biomedical Engineering Society of the Institute of Electrical and Electronics Engineers). Every month, 25 to 75 doctors and engineers met for a technical program. We strove to attract equal numbers of doctors and engineers. Our chapter had a standing offer to send an engineering team to assist any doctor who had an instrumentation problem. One day, I went with such a team to visit Dr. Chardack at the VA hospital on a problem dealing with a blood oximeter. Imagine my surprise at finding that his assistant was one of my old high-school classmates, Andy Gage (afterwards chief of staff at the hospital)! Our visting team couldn't help Dr. Chardack much with his blood oximeter problem, but when I broached my pacemaker idea to him, he walked up and down the lab a couple of times, looked at me strangely, and said, "If you can do that, you can save 10,000 lives a year." Three weeks later, in April of 1958, Bill Chardack, Andy Gage, and I had our first model cardiac pacemaker implanted in a dog.

Our experimental work was done on dogs that had been put into complete heart block by occluding the AV bundle with a tied suture, as taught by Starzl. We had no heart-lung machine. The operating team stood poised like a runner waiting for the starting gun. Upon a "go" signal, the team occluded the large vessels, opened the heart, occluded the AV bundle with the tied suture, closed the heart, and released the large vessels, all with some 90 seconds!

We were pretty naive about early pacemaker designs. We initially thought that wrapping the module in electric tape would seal it. We soon found, however, that any void would fill with fluid, so we began to encase our electronics into a solid epoxy block. Within a year, we had worked our animal survival time up from 4 hours to 4 months and felt ready to start looking for a suitable patient.

The time needed to build the pacemaker units began taking more of my time than my job would allow. My employer at the time, Ralph Taber of Taber Instrument Corp. in North Tonawands, New York, was unwilling to jeopardize his million-dollar company on a liability like the pacemaker, especially after Lloyd's of London had turned him down on liability insurance. So, I decided to quit my job to work full time on the pacemaker and on some astronaut instrumentations that we were building for the early animal space shots.

I had $2,000 in cash and enough to feed my family for 2 years. I put it to the Lord in prayer, quit all my jobs, and devoted my full time to the pacemaker. I gave my family money to my wife. Then I took the $2,000 and went up into my wood-heated barn workshop. In 2 years, I had made 50 pacemakers, 40 of which went into animals and 10 into patients. We had no grant funding and asked for none. The program was successful. We got 50 pacemakers for $2,000. Today, you can't buy one pacemaker for that!

The 10 patients had their pacemakers implanted by Bill Chardack and his associates. Most of the patients were older people in their sixties, seventies, and eighties, typical of the usual heart-block patient. However, two of the patients were children and one was a young man with a wife and two children. The young man, I remember, had worked in a local rubber factory until he collapsed on the job one day. Soon thereafter, he had another severe attack in which his mother-in-law applied resuscitation and brought him back.

Prior to implantation, the young man's prognosis was grim. After recovery, he retrained as a hairdresser, worked full time, and joined a bowling team. This man is still alive and well in 1986. Another patient I remember well, also in complete heart block with Stokes Adams syndrome, was a woman in her sixties. She was our seventh patient. A few years ago, when our local engineering society named me "Engineer of the Year," she came to my award dinner. The news media called her the "Pacemaker Queen." She died, not too long ago, in her eighties, after having been paced over 20 years.

I think one of my first and most gratifying realizations of what a cardiac pacemaker could do came in observing the reactions of elderly patients to their grandchildren. When in block, these people generally didn't have enough blood supply to their brains and couldn't respond quickly to the bantering of the kids. The kids would say, "Well, grandpa's dottery," and go off about their play. With a pacemaker, grandpa could snap back at the kids and be in the mainstream again. I think this, more than anything else, changed their lives. Now that I am (five times) a grandfather myself, I fully realize the impact of what I saw.

We had been aware that the Medtronic Co. in Minneapolis had been working on external, hand-held pacemakers. We learned of this both through Norman Roth and Jim Anderson of Medtronic and through Dr. Chardack's friendship with the Minneapolis heart surgeon Dr. C. Walton Lillehei. We had learned of silicone rubber and medical adhesive through Norm Roth, and the first electrodes we used clinically were the Medtronic electrodes that he and Dr. Sam Hunter had designed.

At the time, Medtronic was still a very small company located in a garage in Minneapolis. The company's president, Earl Bakken, the president, was an electrical engineer. Earl's fiancee Connie was a technician for Dr.

Lillehei, and while waiting for Connie, Earl would wander around the lab and occasionally talk shop with him. Dr. Lillehei, who was then doing some of the first open-heart surgery on children, had occasionally run into cases of complete block in children and adopted the practice of leaving electrode wires temporarily in place after surgery. One time, a power failure incapacitated the line-operated stimulators for Dr. Lillehei's patients, and following this near catastrophe, Earl Bakken decided to build a hand-held, battery-operated stimulator to drive the electrodes. Soon thereafter, Medtronic was building hand-held, battery-operated stimulators in quantity. The income from the stimulators supplemented the company's income from selling Sanborn (now Hewlett-Packard) ECG machines and from occasionally repairing TV sets, when things really got slow.

Financial support for the early ventures was provided by Palmer Hermundslie, a local lumber dealer married to Connie's sister. Palmer also assumed responsibility for all new construction. Unlike other early pacemaker companies, whose growth was stunted by inadequate planning and lack of facilities when they were needed, Medtronic always seemed to have the buildings and the benches ready just when they were needed and rarely had to tell a doctor it couldn't deliver a pacemaker. I attribute most of this superb planning to Palmer. Jim Anderson, himself a capable design engineer, was Medtronic's sales manager and was ever on the road in the company plane selling something to somebody. Norm Hagfors and Bob Wingrove, both former Sunday school students of Earl Bakken, headed up the engineering, and Ron Gymrek handled quality control. This was the team.

In early 1961, Jim Anderson and Palmer Hermundslie (both pilots) flew into Buffalo from Minneapolis. At a luncheon table in the Airways Hotel at the Buffalo airport, we worked out a license agreement. The next day, we had

it notarized at a local bank. I don't know that the agreement was ever formalized into legal language, but it was the beginning of the Medtronic "Chardack-Greatbatch Implantable Cardiac Pacemaker," which dominated the field for the next decade.

The license agreement was a very tight one. I assumed design control for all Medtronic implantable pacemakers. I signed every drawing, every change, and had to approve every procurement source. The device had to be called a "Chardack-Greatbatch Implantable Cardiac Pacemaker" in all company brochures, advertising, and communications, both within the company and without. The quality control program reported directly to me for 10 years. I sat on the board of directors. I had a major (and noisy) input to all company affairs, pushing pacemakers and dropping unprofitable product lines like cardiac monitors and defribrillators. Medtronic had been in a precarious financial situation in 1960, but substantially recovered within 2 years and became number one in pacemakers. Today, two decades later, Medtronic is still number one, but now with a sales volume of nearly $300 million a year.

I made monthly trips to Minneapolis to monitor the product line, to go over quality control records with Ron Gymrek, to sign off drawings and changes, and to attend board meetings. Bill Chardack was just as active as I, but in an unofficial, behind-the-scenes way. It was his papers, his case reports, his spring-coil electrodes, and his personal recommendations that really "sold" the Medtronic device to the profession. Chardack's professional stature and reputation in the field were unparalleled. I still say he was Medtronic's most effective and most credible salesman in those early critical days.

We soon found that the highest grade military components were not good enough for the "zero defect" requirements of pacemakers. The warm, moist environment of the human body proved to be a far more hostile environment than outer space of the bottom of the sea. We had predicted a 5-year pacemaker in our first 1959 paper. Even by 1970, we were only getting 2 years!

We spent most of the 1960s expanding the quality control program. Quality control included 100-percent testing and traceability of component lots. We also instituted a 30-day heat/mechanical shock cycle on transistors and 100-percent X-ray analysis of batteries and completed pacemakers.

The miniature DOT-1 transformers that we used initially were wound with exceptionally fine wire and proved troublesome. The UTC Co. made a special high-reliability model with a double encasement, but we continued to experience failures until we finally went to a transformerless design. The Medtronic 5862 (my last design for Medtronic) used a three-transistor, transformerless, complementary multivibrator circuit (after Roger Russell's patent) which could not "hang up." With diode-isolated, dual-battery packs and voltage-doubler output, it was probably the most reliable of the mercury-powered pacemakers of the 1960s. I was so intent on achieving rate stability that I didn't even include an end-of-life indicator in the design. Some of these units lasted close to 5 years, after which they had to be prophylactically removed because there was no way of knowing how much battery life was left.

Our epoxy encapsulant contracted upon curing, putting pressure on diodes and capacitors and sometimes crushing them. This problem was solved by dipping each component into a silicone medical adhesive thinned with heptane, thus covering each component with a protective silicone rubber sheath. Tantalum capacitors failed occasionally. We finally replaced individual

capacitors with banks of four series-paralleled capacitors so that at least two simulataneous capacitor failures would be needed to incapacitate a pulse generator. Embarrassingly enough, with the additional exposure, the reliability proved worse.

Early transistors were inconsistent. We first used the old solder-sealed TI 910 transistor, then a welded GE 2N335, then a Transitron 2N543, and finally a 2N718A. We identified several failure modes due to contamination and leaky seals. We adopted the policy of segregating the transistors into beta (current gain) classes, then heat-soaking them for 500 hours at 125°C with five cycles to dry ice during this period. Any transistor that developed leakage or drifted more than one beta class was discarded. This was followed by a shock test. We lost about 15 percent of the GE 2N335 transistors in this program, but never lost one subsequently in a pacemaker. (It is interesting to note that the "Minuteman" space program for high-reliability missile components later adopted much the same program after we published our procedures.)

Many of the early Medtronic programs were first worked out at my house in Clarence, New York, and then taken to Minneapolis. I had two ovens set up in my bedroom. My wife Eleanor did much of the testing. The shock test consisted of striking the transistor while under test, with a wooden pencil, while measuring beta (current gain). We found that a metal pencil could wreck the transistor, but a wooden pencil could not. Many mornings, I would awake to the cadence of Eleanor, tap, tap, tapping the transistors with her calibrated pencil. For some months, every transistor that was used worldwide in Medtronic pacemakers got tapped in my bedroom.

In 1964, Barough Berkovitz (also a member of our Professional Group in Medical Electronics chapter when the American Optical Co. Medical Electronics Division was in Buffalo) published a series of papers on a new pacemaker concept in which the pacemaker "listened" to the heart and worked only when the heart didn't. The pacemaker worked only on demand and came to be known as a "demand pacemaker." This seemed like quite a good idea, and we ourselves began working on an implantable version. My laboratory notebook says that we completed our first successful breadboard on January 10, 1965. This design went on to become the Medtronic Model 5841, which was the first implantable, inhibited demand pacemaker to become commercially available.

The design was unique in that it used a very low input impedance of 5,000 ohms. My feeling was that we should match the impedance of the heart to get the best possible QRS input signal, so I used a grounded-base transistor for the input stage. It was a successful design which stayed on the market for some years, but was engineering heresy in that conventional wisdom would tend toward high input impedance rather than low. In fact, all pacemaker designs since have used high input impedance. I'm not sure the change was a good one.

Another unique feature was the lack of any built-in refractory period. The high surface capacity of the plantinum electrode provided an electrochemical refractory that was quite effective, if imprecise.

The circuit was the ultimate in simplicity, with only six transistors. It was always our practice to get the most we could out of the fewest number of parts. Dick Frazier, one of the "old-timers" at Cornell Aeronautical Laboratory, always said, "The best way to keep a part from failing is not to put it in in the first place!" I guess that philosophy has gone by the board now. Modern pacemaker designers think nothing of putting 100,000 transistors into a design.

These were times of considerable stress. We were still working out our designs and procedures, and Bill Chardack and I were not always in agreement on what should be done. At times, we had some pretty harsh words. Time has mellowed all that, and now I can more fully appreciate all he did. In my opinion, William Chardack was the epitome of all a doctor should be. He was an excellent surgeon, physician, and chemist. His concern for his patients was legendary. Many a patient is alive today because of both his formal and his intuitive knowledge of drugs and blood chemistry and his unwavering commitment to see a patient through.

We gradually worked our reliability up to the point where the battery quality became our limiting factor. It became increasingly apparent that we would never achieve our objective of a "lifetime pacemaker" with the zinc-mercury battery. I encouraged Earl Bakken to set up his own battery facility, because I felt sure his suppliers would never do what needed to be done. Although Earl finally took my advice, it was not until over 5 years later!

In the meantime, therefore, I terminated my license with Medtronic (under friendly circumstances) and established my own battery manufacturing company, Wilson Greatbatch Ltd. Battery manufacturing, by the way, was a field which I knew nothing about.

At Wilson Greatbatch Ltd., we looked into several types of batteries. We ruled out biological batteries because of their low energy density and their inconsistent performance. We discarded rechargeable batteries because their battery life <u>with</u> recharging was less than the battery life of our primary batteries <u>without</u> recharging. We put an intensive 2-year effort into atomic batteries, but finally discarded them because of the unacceptability in the clinical situation of the restrictive regulatory requirements on patient mobility and physician reporting.

In 1970-1972, we finally settled on a battery with a lithium anode, an iodine cathode, and a solid-state, self-healing, crystalline electrolyte. The development of the lithium battery eventually removed the battery as the limiting factor in pacemaker longevity. Today, nearly every pacemaker uses a lithium battery of some sort, and nearly every surgical intervention for a pacemaker problem is electrode-related rather than battery-related.

The first half-decade of pacemaking culminated in a "gathering of the clan" at three meetings in the mid-1960s. A symposium in Buffalo in 1965 drew all of the world's pacemaking pioneers: Lagegren from Sweden, Sven Effert from Germany, Lillehei from Minneapolis, Kantrowitz from New York, and many others. Two meetings sponsored by the New York Academy of Sciences in 1964 and 1969 similarly drew a worldwide participation. These three meetings established pacemaking as a universally accepted procedure and cleared the way for rapid progress, both in the technical level of the apparatus and in the spreading of the word to the general practitioner. Hans Lagegren, in a 1978 paper, reviewed the accomplishments of the Karolinska group and recalled our Buffalo meeting where he was able to present the cases of 305 pacemaker patients from five European clinics. He expressed fear that people would forget the things that the pioneers had done.

No, Hans, many of us remember, and we will never forget.

VIGNETTE #9

THE INVENTION OF THE RECHARGEABLE CARDIAC PACEMAKER

Robert E. Fischell, M.S.
Chief of Technology Transfer
Applied Physics Laboratory
Johns Hopkins University
Laurel, Maryland

ORIGIN

The idea for a rechargeable cardiac pacemaker came to me in the late 1960s as the result of reading an advertisement in the magazine of the Institute of Electrical and Electronics Engineers. The ad was placed by the Mallory Battery Co. and stated that the company's batteries were so good that they would last as long as 2 years in a heart pacemaker. It dawned on me that if the batteries had only a 2-year life expectancy, pacemaker patients would have to undergo surgery for their replacement on a very frequent basis.

Having worked on electric power systems for spacecraft at the Johns Hopkins Applied Physics Laboratory (APL), I had devoted considerable effort and a goodly amount of the National Aeronautic and Space Administration's (NASA) money to the development of hermetically sealed, nickel-cadmium batteries that could function for a decade or longer in an orbiting spacecraft. By the late 1960s, the technology for these nickel-cadmium batteries had advanced to the point where one could expect the batteries would perform reliably as a power source for an implantable cardiac pacemaker for a decade or longer. Space technology had made such a development possible.

To show the cardiologists at Johns Hopkins Hospital that a pacemaker of indefinitely long life and having a much smaller size and weight could be readily built, we built the first prototype of a rechargeable cardiac pacemaker at APL in about 1968. Building the first model of a nickel-cadmium-battery-powered rechargeable pacemaker took only a week because the nickel-

cadmium-battery technology was already well known at APL. The pacemaker problem in fact was less difficult than the problems typically encountered on our satellites, so we had more than sufficient technical information to build the model.

Because of the freedom at APL, a very small job like building a prototype rechargeable pacemaker can be done without requiring any specific financial allocation. In order to obtain high-quality, hermetically sealed, nickel-cadmium cells of the type used on spacecraft but small enough for a cardiac pacemaker, however, we had to obtain financial support from an outside source. Initial funding of $11,000 to finance the purchase of small, rechargeable nickel-cadmium cells was provided by the City of Baltimore, specifically, by the Baltimore City Hospitals.

DEVELOPMENT

APL's management realized that the rechargeable pacemaker program would succeed only if a commercial company could be found that would take the results of our laboratory's research and development (R&D) and manufacture and market a rechargeable pacemaker product. In the late 1960s, available cardiac pacemakers required 5 mercury batteries to operate; as a result, these pacemakers were large and heavy and had a mean time to failure of less than 2 years. Another problem with these pacemakers was that they could be turned off by the radiation from microwave ovens. APL's analysis indicated that we could make a rechargeable pacemaker with a single nickel-cadmium battery much smaller than even one of the mercury batteries of the extant pacers; thus, the rechargeable pacemaker would be one-third the size and one-third the weight of conventional pacemakers. In addition, we could hermetically seal the rechargeable pacemaker so that its function would not be compromised by

microwave or other radiation. Finally, by applying reliability and quality assurance techniques derived from space technology, we knew that we could dramatically improve pacemaker reliability.

The potential of the rechargeable device was sufficient to encourage an industrialist, Mr. Alfred E. Mann, who was then president of a company supplying APL with solar cells for our spacecraft, to consider forming a corporation to commercialize the invention. The management of APL and Mr. Mann agreed to the formation of a company called Pacesetter Systems, Inc. which would manufacture and market the rechargeable pacemaker.

Some of the early R&D on the device was carried out at APL under the sponsorship of NASA's Space Technology Utilization Office. The total NASA investment was under $100,000. Alfred Mann put considerable sums of his own money into the project and also obtained equity capital from various investors. This resulted in encouraging private investors to invest over $5 million in Pacesetter in an attempt to make a commercial success of the invention.

A patent for the invention was issued in February 1975. This was followed by a second patent issued in June 1975. It is difficult to say whether the patents were essential in protecting the invention. The rechargeable cardiac pacemaker involved a great deal of proprietary information which was carefully controlled, and no other company attempted to make a similar product. The patent protection plus the proprietary technical information helped make the product attractive to Pacesetter. Without patent protection and an exclusive license agreement, it is extremely doubtful that Alfred Mann or any other investor would have put any money into the project.

In the 1960's there were no Federal tax incentives for R&D which might have helped in obtaining development funds. In the R&D phase, the rechargeable cardiac pacemaker was directly supported by Federal funds. Specifically, NASA provided some initial R&D funding and furthermore granted a waiver of Federal rights so that APL could more readily license the product on an exclusive basis. Other support included the $11,000 provided by the Baltimore City Hospitals and a $6,000 grant from the American Heart Association.

The rechargeable cardiac pacemaker was offered for commercial sale in 1973, 3 years prior to the enactment of the 1976 Medical Device Amendments to the Food, Drug and Cosmetic Act. Thus, the Food and Drug Administration (FDA) was not at all involved in the approval of the first human implants. Nevertheless, APL and Pacesetter proceeded with extreme care to ensure that the pacemaker would be safe and efficacious in use. Furthermore, the first implants had to be approved by APL's Biomedical Devices Committee and by the Joint Committee on Clinical Investigations of the Johns Hopkins School of Medicine. These committees are at least as demanding as FDA is with respect to granting approval for human implants.

MARKETING

The strategy Pacesetter used to market this invention was to hire some direct salesmen and some independent marketing representatives to sell the rechargeable pacemaker to cardiologists and thoracic surgeons. Many of the salespeople Pacesetter employed had experience in pacer marketing from prior employment with other pacemaker companies, namely, Medtronics, Inc. and Cordis Corp.

Since the average age of pacer patients is 68, Medicare reimbursement was and is extremely important in the development of the pacemaker market. Also, physicians in foreign countries were, as they should be, tremendously impressed with American pacemaker technology. Therefore, the foreign markets for the rechargeable and other pacemakers have been and continue to be important.

Now more than 10 years after the first implant, rechargeable cardiac pacemakers are still functioning in hundreds of patients, thus achieving the product's design goal. In 1978, however, Pacesetter's discontinued the manufacture of rechargeable pacemakers. One reason was the development of the lithium battery, which was very much superior to the mercury battery with respect to energy density (i.e., small size with a lot of energy) and reliability. A second significant factor which led Pacesetter to discontinue manufacturing was that the opinion leaders on pacemaker therapy were initially opposed to the rechargeable pacer concept. I believe that this opposition stemmed from personal pecuniary interests of the physicians involved. Since more than 50 percent of the physicians' income was from the surgical replacement of pacemaker devices, these physicans were probably reluctant to accept a rechargeable pacemaker that would halve their personal income. Physicians of lesser stature were then persuaded by these opinion leaders to continue to use conventional pacers whose life expectancy was considerably shorter. In fact, one leading pacer implanter told me that although the rechargeable pacer was technically superior to conventional pacers, pacemaker replacement surgery was very easy and he had a yacht to support, so he would continue to use pacers with a 2-year life expectancy.

Despite the fact that the rechargeable cardiac pacemaker is no longer manufactured, Pacesetter and other new pacemaker manufacturers do use the techniques that we taught on applying reliability and quality assurance techniques derived from space technology to improve pacemaker reliability. They have also adopted our techniques for hermetically sealing the entire outer surface of the pacemaker to preclude electromagnetic interference.

VIGNETTE #10

THE DEVELOPMENT OF A TOTALLY IMPLANTABLE DRUG-INFUSION PUMP

Perry J. Blackshear, M.D., Ph.D.
Associate Investigator
Howard Hughes Medical Institute
Massachusetts General Hospital
Boston, Massachusetts

INTRODUCTION

This paper describes the invention and development of a totally implantable drug infusion pump for use in animals and humans. The device was first conceived by investigators at the University of Minnesota in August 1969. A patent for the device was issued to the University of Minnesota in May 1973[1]. The first clinical implantation of the device was in October 1975, for heparin infusion; subsequent human implantation, in June 1977 and September 1981, for chemotherapeutic agent infusion and insulin infusion, respectively, also at the University of Minnesota; and a patent licensing agreement between the University of Minnesota and Metal Bellows Corp., was executed in October 1980.

In March 1982, following a long and arduous development period, the totally implantable drug-infusion pump was approved by the Food and Drug Adminstration (FDA) for the delivery of heparin in patients with refractory thromboembolic diseases and for the intra-arterial infusion of the chemotherapeutic agent 5-flurodeoxyuridine (FUDR). Subsequently, in February 1983, FDA approved the device for the delivery of morphine for refractory pain of malignant origin. In October 1980, the Pump Development Division of the Metal Bellows Corp. spun off to form a separate company, now called the Infusaid Corp., located in Norwood, Massachusetts. According to company

[1]Perry J. Blackshear et al., Implantable Infusion Pump, U.S. Patent #3731681.

sources, there had been approximately 6,000 human implantations worldwide as of September 1983. A bibliography of articles from the University of Minnesota group describing the device and its use in animals and humans is available from the author.

ORIGIN

The idea for development of an implantable drug-delivery device was not new. Attempts at implanting drug-dispensing devices in both human and animal bodies had been carried out since the early 1930s. The devices used, however, were not useful for delivering macroscopic quantities of commercially available drugs into the human body. For the most part, they consisted of erodible pellets that would gradually break down over time to release drug into the space under the skin or other tissue spaces, or semipermeable polymeric capsules which would allow slow diffusion of minute quantities of drug into the same tissue spaces.

The need for a larger drug-delivery device was initially identified in 1969 by Dr. Richard L. Varco, then professor of surgery at the University of Minnesota and subsequently one of the pump's inventors. At that time, a prevailing theory held that heparin, a naturally derived anticoagulant substance with a long history of use as a drug in human beings, if delivered slowly and continuously over long periods of time, might prevent or delay the development of atherosclerosis (hardening of the arteries) in susceptible individuals. Dr. Varco reasoned that if one could develop a means of infusing heparin into the ambulatory (i.e., nonhospitalized) patient for long periods of time, one might be able to achieve these beneficial effects on the development of atherosclerosis without the need for continuous hospitalization. His idea was to use one of the methods previously developed

by Dr. Judah Folkman, which involved diffusion of anesthetic agents and other drugs through silicone rubber barriers, by means of, for example, an arteriovenous shunt.

In 1969, I was hired to work as a summer student in Dr. Varco's laboratory, and my assignment was to investigate the use of silicone rubber polymers and other diffusion systems then available as a means of delivering heparin continuously at a steady rate into an ambulatory animal or patient. After a series of initial experiments, it became obvious that heparin, because of its extremely large size and powerful negative charge, could not be induced to diffuse through silicone rubber. Attempts to measure heparin's diffusion through other polymeric membranes also failed. It became evident that for heparin and other drugs with unusual size and charge properties, a macroscopic drug-delivery device such as an infusion pump might be the best way to accomplish delivery. Thus, in discussions with Dr. Henry Buchwald, in whose laboratory I was carrying out these experiments, Dr. Varco, Dr. Perry L. Blackshear, Jr., my father, a professor of mechanical engineering at the University of Minnesota, and Frank D. Dorman, another mechanical engineer, the idea of a totally implantable drug-infusion pump was born.

Out of these preliminary discussions arose essentially all of the ideas for the components of the first prototypes and indeed the eventual commercial device. A major thing that made the device possible was the simple physical principle that a vapor in equilibrium with its liquid phase exerts a constant vapor pressure on its surroundings, regardless of the enclosing volume. This principle, and the fact that the temperature of the human body is maintained at a very contant level under normal circumstances, made possible the concept of the pump's vapor-liquid chemical power source. In order to have a vapor-liquid power source, it was necessary to find a chemical substance that would

produce a sufficient vapor pressure at body temperature to overcome the variability imposed by changes in venous and arterial blood pressure, yet be nontoxic and noncorrosive to the pump components. Several agents, including diethyl ether and tetramethyl silane, were tried in initial prototype devices, but by late 1970, the use of a nontoxic, noncorrosive fluorocarbon as the source of the driving vapor pressure had become established.

Clearly, since the power source was a vapor-liquid mixture, it would have to be separated from the drug reservoir against which it exerted pressure by a totally impermeable barrier. Many forms of collapsible barriers were discussed and then discarded. Polymeric, plastic, and rubber membranes were discarded because of concerns that over time, these barriers would not prevent the diffusion of gas from the power source into the drug chamber with resulting change in its properties and loss of driving vapor pressure, or would not prevent the diffusion of drug into the chemical power source chamber. Over the expected life of the pump, which even in the earliest stages of development was envisioned as many years, an absolutely impermeable barrier between the power source and the drug chamber was mandatory.

The concept that made this possible was that of a collapsible metal bellows, which would have the collapsibility characteristic of a rubber membrane, but still be totally impermeable to both gas and liquid and not subject to corrosive influences from either. The requirement for such a bellows led us to investigate the current bellows manufacturers in the United States. This investigation eventually led us to the Metal Bellows Corp. of Sharon, Massachusetts, which at that time was one of the few manufacturers of precision welded bellows in the country. Welded bellows were deemed necessary because of the low, constant spring rate which they have, in comparison to formed or molded bellows. The first prototypes, therefore, were built with

off-the-shelf stock bellows from the Metal Bellows Corp. (Subsequently, as described below, this company's involvement in the development of the pump increased.)

Other technical components that were necessary to complete the device design were a self-sealing silicone rubber/teflon stopper or septum which was available from commercial sources, a special needle to permit puncture of the septum many times without causing damage to the septum, and a long, narrow-bore stainless steel or titanium capillary tube to serve as the flow-regulating resistance element. These components, as well as biocompatible metals and silicone rubber polymers for use in long-term implantation in the body, were commercially available at the time of the pump's development and made possible a biocompatible and functioning prototype in the very earliest stages.

The first prototypes of the pump were built and tested in vitro at the University of Minnesota in September 1969. The first animal implantations were performed there in January 1970. The first public description of the device, its design, and initial experimental results at the American College of Surgeons in Chicago in November 1970. The earliest bench tests and animal studies demonstrated that the device was capable of providing constant drug infusion rates at constant temperatures such as those prevailing under the skin of an animal or human patient and it was evident that the potential uses of such a device for the drug treatment of various disease states in humans were myriad. For these reasons, we thought that it was appropriate to patent this device and begin a search for possible commercial licensees.

Therefore, in the fall and winter of 1969 and the spring of 1970, when the first prototypes were built in the mechanical engineering shops at the University of Minnesota and later in the hospital machine shop at the

University of Minnesota Hospitals, no commercial company had yet been involved in the development of this device except to supply stock component parts for the device. Going from the concept of the device to the first functioning prototypes was not particularly difficult, given the engineering expertise and experience with biocompatible materials of Mr. Dorman and Professor Blackshear, the awareness of the surgical requirements of such a device by Drs. Buchwald and Varco, and ability to test the initial prototypes in the dog labs in the department of surgery at the Unviversity of Minnesota. Once we had identified commercial sources of the various components and decided which off-the-shelf components might be appropriate, the development and testing of the first prototypes proceeded without much difficulty. By that time, I had been hired as a technician at the University of Minnesota while finishing my junior and senior years of college, and the other inventors were salaried staff members at the University of Minnesota. Financing for the development of prototypes came from a variety of sources, including Minnesota Medical Foundation Scholarships, private department of surgery sources, and some Federal grant money awarded to Drs. Buchwald and Varco for research into the prevention of atherosclerosis.

DEVELOPMENT

The patent disclosure for a totally implantable drug-delivery device was filed through the University of Minnesota in May 1970. By this time, it had become clear that the device could deliver heparin at a constant rate into the vascular system of animals, and potentially of humans, for long periods of time, and thus might be a useful therapeutic tool. Since this was the first device of this type of which we were aware, it also became evident that a much wider range of drug therapies might be useful using this pump as a drug delivery vehicle.

The decision to proceed beyond the prototype development and into possible eventual commercial usage was made as a more or less consensual agreement among the inventors, the patent officials at the University of Minnesota, and informal advisors. The decision was based on the early results with the device, in response to informal contacts within the medical community, and on the response to the first scientific presentation of our data in November 1970. We had no interest at that time in forming a company to manufacture and distribute the pump. It had also become clear that a very long research and development (R&D) period would be necessary before the first clinical implantations of the device would be possible. For this reason, we began looking for companies that would be willing to expend a large R&D effort for many years without expecting a profit in the near term. The patent disclosure and application had been filed through the University of Minnesota and it seemed appropriate to begin making commercial contacts for the possible eventual marketing of a clinically usable device.

We instituted contacts with several medical device organizations and held lengthy discussions with Medtronic, Inc., a large Minneapolis cardiac pacemaker firm because of the company's proximity and its long experience with marketing implantable devices. However, on the basis of a marketing survey and other considerations, Medtronic decided against becoming involved with pump development at that time (late 1970). One or two other pacemaker firms were approached with equal lack of success.

I then wrote to the Metal Bellows Corp., with whom we had enjoyed an amicable relationship based upon our use of their standard off-the-shelf bellows for prototype construction. My letter was brought to the attention of the company's president, Raymond Shamie, who became intrigued with the possibility of manufacturing a medical device based on welded bellows

technology and contacted us immediately. A series of discussions ensued among the University of Minnesota, the inventors, and the Metal Bellows Corp. The university and Metal Bellows Corp. signed an option agreement in April 1971, in which the company agreed to provide certain funds for R&D during the early animal and clinical phases of device development at the University of Minnesota in return for future exclusive manufacturing rights. At that time, Metal Bellows Corp. did not have any medical device manufacturing or marketing expertise, but the company's management believed that this expertise could be acquired during the (predicted) long R&D phase.

From 1971 to 1975, the pump was refined as a joint effort between the University of Minnesota, under the direction of Henry Buchwald, and the Metal Bellows Corp. The initial prototype construction was improved to accomplish several design requirements, including ease of implantation, decrease of the bellows spring rate, decrease of the flow rate, inclusion of a biologically compatible chemical power source, and other modifications. In addition, during these 4 years, extensive, long-term animal trials, involving the infusion of intravenous heparin or saline into approximately 30 dogs, were carried out at the University of Minnesota Hospitals. These animal studies were performed to test the safety and effectiveness of the device before proceeding with the clinical implantation of the device for heparin infusion. In addition, preliminary studies were carried out using the pump as a means of delivering the chemotherapeutic agent FUDR into the hepatic artery for the treatment of inoperable liver cancer, and as a means of infusing intravenous insulin in the treatment of patients with diabetes mellitus. During this initial R&D phase, no Federal funds were directly involved in the testing of the device, although Federal funds were later acquired during some of the clinical trials. As mentioned above, a patent was issued to the University of Minnesota in 1973.

In 1975, after several years of experience in animals in which both heparin and bacteriostatic water had been infused intravenously with success, the decision was made to proceed with the first clinical implantation of the pump. Accordingly, this implantation occurred at the University of Minnesota Hospitals on October 22, 1975, and was performed by Dr. Henry Buchwald and his staff. The first patient was a middle-aged woman with severe thromboembolic disease with recurrent pulmonary embolization which was refractory to therapy with warfarin, an oral anticoagulant. The surgical implantation was uneventful, and the pump functioned perfectly for the 1 year it remained implanted. The pump was removed from this patient after 1 year because of her significant weight loss and evidence that her refractory clotting problem was no longer active after 1 year of treatment.

When it became obvious that the first patient was doing well with the implanted pump, a number of patients with refractory clotting problems underwent pump implantation for the infusion of heparin. These studies were continued for several years and were published in 1980 in Surgery. These studies established in humans, as the animal studies had indicated previously, that the pump could be implanted under the skin safely and without significant morbidity; that it could be left in place for at least several years; that continuous, constant rate drug infusions could be carried out by this means; and that the refills could be accomplished at reasonable intervals with mimimal patient discomfort--in short, that this pump could be used as a totally implantable drug-delivery system in humans.

Very quickly thereafter, the device R&D effort branched into several new categories. The heparin study was expanded to include patients with severe arterial clotting problems, especially those of the cerebral circulation. After extensive animal testing of the pump as a means of

infusing the chemotherapeutic agent FUDR into the canine arterial circulation, Dr. Buchwald obtained a grant from the National Cancer Institute (NCI) to support testing of the device as a means of providing intra-arterial infusion chemotherapy in patients with inoperable primary or secondary liver cancer. Under this grant, a series of five patients received implanted infusion pumps for the infusion of FUDR into the hepatic artery at the University of Minnesota Hospitals beginning in 1977. These studies demonstrated that the pump could be used as a means of infusing FUDR in these cancer patients with minimal patient morbidity associated with the device itself. (The infusion of FUDR is currently the major clinical application of the device.) Finally, a large series of animal tests were begun and continued to the present time, the ultimate aim being to demonstrate the usefulness of this device as a means of infusing insulin into animals and eventually human patients with diabetes mellitus. Again, most of the R&D costs during this phase of testing were born by the Metal Bellows Corp. although, as mentioned above, the initial clinical trial involving cancer patients was funded by NCI.

During these early studies, FDA was involved through the mechanism of the investigational device exemption (IDE). In general, it was our impression that FDA did not impose undue restrictions on the experimental use of this device in humans.

In October 1980, the Pump Development Division of the Metal Bellows Corp. spun off to form a new company called the Infusaid Corp. for the purpose of manufacturing and eventually marketing the implantable drug infusion pump (now known as the Infusaid Implantable Infusion Pump). Although IDEs had been filed by Dr. Buchwald and other investigators, after the passage of the Medical Device Amendments of 1976, Infusaid was responsible for obtaining the premarket approval from FDA. Therefore, my involvement with FDA, and the

involvement of the other inventors and investigators, was necessarily somewhat limited at this point, although most of us were involved in testimony before FDA prior to approval. My impression of FDA throughout these dealings was that the agency was sincerely trying to carry out its mandate, was not unduly restrictive in requiring proof of safety and efficacy, and, in general, behaved as a regulatory agency should behave. After having previously acquired the general impression that FDA was unduly restrictive in permitting the marketing of drugs in the United States, I was pleasantly surprised with my experiences with the device branch of FDA.

Since many of the restrictions imposed on device manufacturers came into being in the late 1970s and were not around during much of the time that the implantable infusion pump was being developed, they had a relatively limited impact on the initial development and testing of the device. I believe that we would have proceeded with its development regardless of whether or not FDA regulated the marketing of medical devices. The long years of animal and early human testing would have been necessary to satisfy our own consciences and the scrutiny of the medical comunity with respect to the safety and efficacy of an implantable device; my feeling is that the FDA requirements which eventually came into being were similar to the requirements self-imposed by the University of Minnesota and Infusaid Corp.

MARKETING

After the premarket approval by FDA, the Infusaid Corp. was permitted to market the device, initially for FUDR and heparin infusion and later for morphine infusion. As one of the inventors, I have not been directly involved in marketing decisions or strategy. However, the pumps are being marketed both in this country and abroad at the present time, and the sales of the

device for the uses just mentioned are continuing. Meanwhile, considerable R&D effort is being expended on the development of modified devices suitable for insulin delivery and other experimental applications.

CONCLUSIONS

I have tried to summarize some of my experience during the development, testing, and eventual commercial marketing of a totally implantable drug-delivery device. In retrospect, there are several things about this story which strike me as worthy of comment. The first is that, to my knowledge, no mechanism existed for the transfer of technology from the University of Minnesota academic laboratories to commercial firms. The university patent office was useful in the patent application process, so that minimal expenditure was required on the part of the inventors (in return, the university receives a large share of the royalties from the license of the patent). However, there existed no industrial liaison office to assist us in our industrial contracts. These contracts were initiated privately by us, probably in an extremely inefficient manner, and resulted in eventual commercialization of the device through good luck, among other things. I presume that in this era of more widespread university-industry ties, especially in the general area of biotechnology, university-industry liaison offices have been established to make this process easier for naive and inexperienced inventors.

The second major thing that strikes me about this story is the extremely long and very expensive R&D process that was required between the initial conception of the device and its reduction to practice and eventual commercial sales. The process would probably not have been possible without the friendly involvement of the Metal Bellows Corp. from the earliest stages

of development, and their dedication to the device and their goal of eventual commercialization. I suspect that the inability to support long-term R&D projects has prevented many smaller companies from entering the medical device field.

Finally, it is very interesting to me to note that, within the last several years, several other totally implantable drug-infusion pumps have been developed, many of them relying on our early work for the proving of certain components. Currently, the need for and the market for such devices appear evident, whereas 14 years ago, when our device was initially designed, it was viewed as a fairly radical departure from accepted medical practice.

ACKNOWLEDGMENTS

I would like to thank my many colleagues at the University of Minnesota and The Massachusetts General Hospital who have contributed to the work described in this paper. In addition, I would like to thank the Metal Bellows Corporation and Infusaid Corp. for their enthusiastic dedication over the years.

VIGNETTE #11
THE INVENTION OF THE PROGRAMMABLE IMPLANTABLE MEDICATION SYSTEM

R. E. Fischell, M.S.
Chief of Technology Transfer
Applied Physics Laboratory
The Johns Hopkins University
Laurel, Maryland

ORIGIN

The idea for a programmable implantable medication system (PIMS) occurred to me in late 1975, when I was conceiving of uses for implantable devices beyond cardiac pacemakers (see story #8). The first prototype of PIMS was developed at the Applied Physics Laboratory (APL) of Johns Hopkins University, where I had the position of Chief of Technology Transfer in the Space Department.

To make an implantable medication infusion system possible, it was necessary that microchip technology be developed to a reasonably high state of sophistication. A specific requirement was the availability of very low power usage CMOS (complimentary metal oxide silicon) chips, RAM (random access memory), ROM (read only memory), input/output chips, and chips for peripheral digital circuitry. Furthermore, the art of microminiaturized fluid-handling systems operating on microwatts of power for the pumping of liquids had to be developed. In fact, such development has occurred, and the electronic systems for PIMS require only 10 microamps and the pumping system operates on a daily average of only 3 microamps. A third technological development that was necessary for PIMS was the lithium thionyl chloride bromine-complex battery. This was developed in the early 1980s by Wilson Greatbatch Ltd. and was indispensable to obtaining a least 5-year life for the implanted portion of PIMS.

The problems encountered in going from idea to the first prototype involved obtaining the best microchips available at that time, finding a firm with an expertise in fluid-handling systems, and finding a battery that could power the implanted portion of PIMS for a period of at least 5 years. Technical information on the chips was obtained from a variety of chip manufacturers. Technical information on how to design and fabricate a fluid-handling system was provided by the Air and Space Products Division of the Parker-Hannifin Corp. in Irvine, California. As a result of work on PIMS, Parker-Hannifin formed a separate division called the Biomedical Products Division. Technical information on a long-lived, low-input impedance battery for PIMS was obtained from Wilson Greatbatch Ltd. of Buffalo, New York.

There were many technical problems that had to be overcome once the relevant information was available. An implantable microcomputer, battery, and fluid-handling system for PIMS had to be designed, built, and evaluated. Financing the first prototype was a considerable problem.

An important problem encountered in prototype development was the instability of insulin when used in the implantable pump portion of PIMS. The principal manufacturer of insulin for the United States, the Eli Lilly Co., refused to work with APL on an improved insulin, the reason being that Eli Lilly owned a pacemaker company, CPI, which had aspirations of making an implantable pump of its own. Following Eli Lilly's refusal, I contacted NOVO Labs of Copenhagen, Denmark (the world's second largest insulin manufacturing company after Lilly). I convinced NOVO's management to invest a considerable sum in developing a laboratory at their plant for the creation and testing of insulin for implantable pumps. NOVO agreed to do this on the condition that once the insulin was developed, they would make it available to any organization with a workable pump. In my opinion, Eli Lilly lacked wisdom in restricting the use of any pump insulin it developed to its subsidiary CPI.

Funding

Research and development funds for PIMS came from a variety of sources. The National Aeronautics and Space Administration's (NASA) Space Technology Utilization Office provided funding of approximately $1.5 million. Parker-Hannifin Corp. invested over $4 million in the hopes of eventually profiting from the sale of its fluid-handling system. Wilson Greatbatch Ltd. invested approximately $250,000 in the development of a special cell for PIMS, again in the hopes of marketing that product. Finally, Pacesetter Systems, Inc., expended approximately $900,000 at APL in support of the development of this device. Currently, Pacesetter is expending approximately $2.0 million per year for the development of this product. Additionally, the National Institutes of Health (NIH) provided $2 million for the evaluation of PIMS in laboratory dogs and 16 human subjects for the treatment of diabetes. NIH also purchased $0.4 million of PIMS devices for the study of the treatment of sexual hormone dysfunction.

DEVELOPMENT

Even before the first prototype was completed, PIMS was considered to have such a potentially large market that Pacesetter Systems made the decision to manufacture and market it. A first patent on PIMS was issued in February 1983 with 642 claims of novelty. This patent was the most comprehensive in that regard of any ever issued by the U.S. Patent Office. Two additional patents have now been issued and four other patent applications are pending by APL on various aspects of PIMS. Two other patent applications from Parker-Hannifin are in process. PIMS also involves a considerable amount of proprietary information. The combination of patents and proprietary

information is extremely important in protecting this invention and making the invention attractive to outside sources of financing. Without the patents, financing from an outside development firm such as Pacesetter would not have been available. Furthermore, Pacesetter became a public corporation in December 1983, and is frequently asked by stock analysts, "To what extent do you have patent protection?" A separate company called Minimed Technologies, Ltd. has now been formed to manufacture and market the PIMS systems.

The fact that there is now a research and development (R&D) investment tax credit is to a small extent a factor which makes a company such as Pacesetter invest in the development of an invention such as PIMS. Pacesetter's enthusiasm for continuing and enlarging its R&D efforts is, to some extent, a result of the R&D investment tax credit. As previously stated, Federal funds from NASA were provided during the R&D phase of PIMS. Furthermore, NIH provided funds for clinical trials. Support from voluntary organizations such as the American Diabetes Association was not actively pursued.

APL has had considerable interaction with the Food and Drug Administration (FDA) on PIMS. The first submission to FDA for PIMS occured in October 1983. During four or five different meetings with APL over the last several years, FDA representatives were always cooperative and helpful. Final approval for human implant was given in May 1986.

FDA's regulatory requirements did not deter the development of PIMS. Pacesetter was not deterred from providing capital because it is aware of the necessity of working with FDA. Furthermore, the potential profits to be made from the sale of PIMS outweigh the financial expenditures and general hassles of having to deal with FDA. FDA regulatory requirements had no effect on developmental costs or the characteristics of the device, because both APL and

Pacesetter understand that the efficacy and safety of implantable medical devices must be as great as the existing technology can provide. Safety and efficacy were considered at every design meeting during the development of the PIMS system. APL and Pacesetter's intense focus on making a device that was as effective and safe for patient use as possible resulted not only because we were looking to do something noble or at least correct (although it certainly seems ethically right to make the best device you can), but also because the only way to achieve the best marketability of a product in this competitive world is by making the product as useful and safe as the technology allows. I do not know how to reduce the cost of compliance with FDA regulations while maintaining efficacy and safety requirements.

MARKETING

The market for PIMS was estimated by considering what diseases could be treated more effectively with the device, determining the number of persons in the United States and in the world afflicted by such diseases, and finally by estimating the fraction of such patients who might actually use the PIMS system. The invention was then sold to a company on the basis of an exclusive license. The fact that NASA granted APL a waiver of the Government rights to this invention was very important in being able to sell the invention to Pacesetter. Furthermore, the Bayh-Dole law passed by Congress several years ago allows an automatic waiver of Government rights for APL inventions (because APL is part of a university) for the purpose of licensing such inventions for manufacturing and marketing. In this respect, the Bayh-Dole law was extremely valuable in getting PIMS, developed partly by NIH funds, to be manufactured by a private company so that the results of Government programs can benefit the public.

Reimbursement from Medicare will be important for PIMS, but medical care coverage from health insurance carriers is a more important consideration for this product.

It is expected that PIMS will be marketed in foreign countries. The total foreign market should equal the U.S. market and is therefore very important. Because of Government support, APL was able to develop an innovative product which appears to be superior to anything being developed in foreign countries.

I estimate the product life of PIMS to be approximately 20 years. This estimate is no different from prior estimates for the product.

Since there is not yet any revenue coming in from PIMS, one cannot compare actual with projected marketing results.

GENERAL OBSERVATIONS REGARDING THE DEVELOPMENT OF MEDICAL INVENTIONS AND DEVICES

Listed below are what I believe to be some of the more important aspects of getting medical inventions into public use:

1. In negotiating licenses with manufacturing companies, a government patent policy allowing a contractor to retain principal rights in federally sponsored inventions is definitely an asset.

2. The Federal law allowing reexamination of already issued patents significantly reduces the value of patents because of the delays that result in the Patent Office. I understand reexamination typically takes 2 years. Thus, for that additional time, an inventor can be denied his rights. If the reexamination were required to be completed in 60 days, the law would be less damaging to inventors.

3. A law to protect component suppliers from frivolous medical malpractice suits is badly needed. National Semiconductor and General Electric Co., Battery Division have both refused to sell needed components for implantable medical devices because of the risk that a capricious suit against the marketer of the final product could result in the component manufacturer's becoming a party defendant. Thus, we are deprived of components critically needed for health care. We need a law that asserts that the company that markets the device to the public has full liability risk and that a component manufacturer has liability only if there is a deliberate intention to defraud or falsify performance data pertaining to that component.

4. I strongly recommend that there be no restraint on granting exclusive licensing arrangements for inventions resulting from federally sponsored R&D projects. In the abstract, it sounds better to say that the fruits of Government-sponsored R&D should be available to all. However, no company that I have encountered is willing to risk capital to manufacture and market an invention when if they fail with the product, they lose their investment, and if they succeed, they have to fight it out in the marketplace.

VIGNETTE #12
DENTAL LAMINATE VENEERS

Frank R. Faunce, D.D.S.
Associate Professor of Pediatric Dentistry
Emory University School of Dentistry
Atlanta, Georgia

My idea for dental laminate veneers developed in 1973, when I was a pediatric resident at the University of Texas dental branch in Houston, Texas, and working with handicapped and mentally compromised children from the Rosenberg State School. Because of their illnesses, many of these children had drug-stained, fractured, or disfigured teeth, which gave them unsightly smiles. The cost of cutting down their teeth and capping them with porcelain crowns was great, and such crowns frequently had to be replaced when the patients fell or suffered any traumatic accident. Our budgets at the Rosenberg hospital were limited, and yet, I felt, these children deserved to have normal smiles just like other children. The need, therefore, was for an alternative method of aesthetically restoring the maxillary anterior teeth at reasonable cost.

One morning on the way to the hospital, the idea for a new method occurred to me. Newer and stronger plastic materials and enamel bonding techniques had been developed at the National Institutes of Health and various university dental schools. All we had to do was to develop a thin, durable veneer of this newer plastic and bond it directly to the enamel surface of the tooth. Eliminating the need for an intermediary cast metallic core or crown core would eliminate the need for the painful process of cutting the tooth down. The veneer of plastic need only be moulded to fit the contours of the tooth much as a contact lens is contoured to fit the cornea of an eye. The moulded plastic veneer could then be laminated to the surface of the tooth by

a thin layer of bonding plastic.

The concept was so simple and the technology was new. I could hardly wait to test it on extracted teeth in the dental laboratory, where I could check the bonding strength and impact resistance. The laboratory tests were highly successful, so I tested the concept in my own mouth. Over the next 2 years, I set up a series of human trials with children at the University of Texas and also at the Medical College of Georgia, where I was then an assistant professor of pediatric dentistry. The tests were highly successful, and the results were published in the Journal of the American Dental Association.

After I had developed the prototype and proved it in the laboratory, I set about on my own to obtain a patent on laminate veneers. I was told that companies would never accept anything new unless there was patent protection. I went to the dean of the University of Texas dental branch in Houston with the concept, and he said that the university had no interest in the concept and would not seek any patent. My department chairman, Dr. Richard Jennings, encouraged me to develop the concept myself, so I took the first steps and sought a patent at my own expense. The laboratory trials and initial clinical trials were at my expense. My brother and I contacted all of the major dental manufacturers, and none was interested in developing the concept or spending any money on its development. During the 2+ years of patent applications and development, every one of these manufacturers turned the concept down.

After the patent was granted domestically and it was certain that foreign patents that had been filed were going to be granted, it became apparent to me that the world did not always beat a path to a better mousetrap. Thus, my brother and I decided to manufacture and market the product ourselves. My education was a great asset, since I was familiar with

the published literature pertaining to dental polymer resins and I had a firm background in dental biomaterials.

The major technical obstacle in the development of dental laminate veneers was the creation of an intervening copolymer that would bond to the highly cross-linked and molecularly dense laminate veneer and the Bis-G.M.A. composite bonding paste. I discovered the correct combination of materials after a series of laboratory trial and error experiments with various compatible copolymer agents. After that, everything worked perfectly. All of this research was done at my expense and in my own home laboratory--my kitchen.

The financing for the research, both laboratory and clinical, came from bank loans on both my brother's and my signatures. By this time and after many thousands of dollars of expense, my brother and I had come to the conclusion that we could expect no outside help and that we should market our own products. I called Dr. John Heyde, the Director of Research of the L.D. Caulk Co. in Milford, Delaware, and asked him if he could tell us how much it would cost for L.D. Caulk to manufacture our product as a subcontracter. Dr. Heyde had turned our proposal down several times, so my brother and I were elated when he now showed some interest. He asked if the patents had been granted and when we said that they had, he told us he would call us right back. Within 15 minutes, he returned our call and said that L.D. Caulk might be interested in manufacturing the product, but first the president of the company, Burt Borgelt, wanted to see a practical clinical demonstration of the procedure.

By this time, 3 years had passed and our clinical research had helped us perfect our techniques. Our inquiries to the Food and Drug Administration (FDA) were mostly ignored. FDA officials told us they had no interest in

materials that were already being used in dentistry and were only being applied in a new way. We have since learned from various dental manufacturers that the FDA officials involved with dental manufacturing have for many years taken the stance of making no decisions (politically expedient) since a positive or a negative decision would create a potentially dangerous political position for them. Overall, our experience with the FDA people in Washington was that they were singularly unresponsive. We have been quite unimpressed with the decisionmaking capability of FDA. Agency representatives were not very helpful in guiding us with the research and development (R&D) process. We had to rely upon the suggestions of the human resource committees of the various universities where we did our research.

When Mr. Borgelt and Dr. Heyde visited with us at the University of Texas dental branch in Houston, they appeared to be genuinely impressed with the results of the clinical demonstration and said that they would like to license the product. Mr. Borgelt later confided to me that it was quite rare for the company to license a product from an independent developer but that our development had solved a problem that they had been working on for years and on which the company had invested a great deal of money. He also mentioned that most companies were not interested in any products no matter how good they might be if a marketing edge could not be obtained by patent protection.

The marketing of the product was undertaken by the L.D. Caulk Co. after licensure. We were really never allowed to have any input into the marketing of the product even though we had many suggestions. L.D. Caulk is basically managed by marketing people who have a very limited technical background. Our observations have been that the company generally uses R&D to support management and marketing goals. The company's own research people tend to be

frustrated routinely by decisions made on product development by marketing individuals who don't really fully comprehend the scientific and technical aspects of the products that they are developing and marketing.

Dental laminate veneers were introduced to the dental profession at the annual American Dental Association meeting with a considerable amount of advertising in various dental journals. The product became highly successful with the dental community even though the dental manufacturer had no educational programs to teach private practitioners the proper techniques or to introduce the procedure into the curriculum of the various dental schools. Most dental schools gradually introduced it into their curriculums because of pressure from the private practitioners of this country and abroad. This educational process was facilitated by the continuing education programs that most dental schools have to reeducate dentists in private practice to new techniques and materials.

Only recently have dental manufacturers started to become involved in the educational process. Their approach has usually involved the old-fashioned process of lecture and normal marketing advertising. Because of a lack of cooperation between dental schools and corporations, there are currently no effective hands-on educational programs. Another problem is that antiquated State dental practice acts and licensure procedures make it extremely difficult for dentists to work from State to State. A dentist licensed in one State cannot perform clinical procedures on patients in any other State, even in an educational environment, without taking that State's dental board examinations. Presentation of credentials is not accepted in dentistry as it is in medicine. Of course, this problem with respect to teaching the use of new procedures or materials could be largely overcome if robotic techniques for teaching, such as those currently being developed in several Western European countries, were instituted in the United States.

The laminate veneer or bonding process is now one of the most widely used procedures around the world and has caught the attention of the national news media--both television and printed magazines and newspapers. Frequently because of media exposure (mostly inaccurate), the public is more aware of these newer procedures and technologies than are dental practitioners. Many times, dentists sign up for continuing education courses to learn about a technique or new materials only when a patient asks about it after reading a story about it in the news media or seeing a demonstration or discussion of it on television. At the university, we get many public inquiries following any news story.

I am constantly amazed at the total lack of concern of most dental schools about reeducating dentists in private practice about new techniques and materials and most corporations' inability to educate them. It's no wonder that technology and new developments occur at a more rapid rate than most universities can reeducate dentists in private practice.

Laminate veneers are now being used to provide aesthetically appealing smiles for patients without pain or irreversible tooth damage at a price far below the older crowning procedure. Many individuals in the entertainment industry, modeling, or other occupations that involve public contact are having their teeth laminated. The laminate veneer process was accepted by most insurance companies and had been unive sally accepted by the majority of the practicing dental profession. It is interesting to note that the Federal services have been the last and least to accept this newer and more inexpensive restorative procedure.

The product life currently is approximately 5 to 7 years. This compares favorably with older, more conventional techniques and also compares very favorably with estimates that were made in the early R&D phases. We are

currently conducting research with microstructured ceramic materials that promises dramatic increases in longevity, as well as a decrease in clinical placement time. Thus, we appear to be on the verge of absolutely painless and extremely inexpensive restorative techniques for aesthetic dentistry in the future for both single- and multiple-tooth restoration and bridging procedures.

The revenue/profit projections compare favorably with the marketing experience when that marketing is coupled with dentist and patient education. Education of private dental practitioners in the use of this product and in placement techniques increased sales. When conventional advertising with no corresponding education was tried, sales decreased. For this reason, the L.D. Caulk Co. is currently endeavoring to develop its product education program for professionals and has created an educational division within its marketing section that is headed by a dentist, Dr. Vincent Cammarato, who has research, private practice, and educational experience.

VIGNETTE #13
PLASMAPHERESIS

Edwin Whitehead
Chairman
Whitehead Associates, Inc.
Greenwich, Connecticut

In the early 1940s, I read a provocative article by Dr. Arthur Wright, who I believe was a professor of surgery at New York University. Wright observed that if one removed the plasma from a blood donation and then reinfused the red blood cells in the donor, one could bleed the donor twice a week as opposed to once every 7 weeks.

At the time, we were doing some work with Dr. William Aaronson, a pathologist at Morrisania Hospital in New York who also had a private laboratory. He and I discussed Wright's article and decided that the process would only be practical if it were automated. Otherwise, taking a blood donation, then separating the cells and plasma, and then reinfusing the red blood cells would be too laborious.

This was during World War II, and every newspaper and advertisement cried out for donations of plasma, which was sorely needed for the military. Since most of the soldiers in the United States were young and healthy, Aaronson and I reasoned, bleeding the soldiers twice a week might be a better way of obtaining plasma than depending on donations by the civilian population. Therefore, if we could make a small, portable, rugged, relatively inexpensive device to automate the process described by Wright, the military and Red Cross would have great need for it. Our motives were patriotism, the desire to be of service to mankind, and the opportunity for economic gain, in that order.

Aaronson and I did a considerable amount of experimenting to determine the most efficient way to separate blood and plasma. The design we finally came up with was a cone-shaped container with radially extending blades that divided the container into separate compartments. The procedure was to draw blood through a needle directly into the center of the spinning container. The red cells were packed by centrifugal force at the outer edges of the container while the plasma formed a layer closer to the center. We started removing plasma as soon as we had drawn 100 ml of blood. By the time the 400 ml blood donation was finished, the plasma had been totally removed into a plastic bag. Saline solution was added to the donor's red blood cells, and the cells were fed back to the donor by gravity through the same needle used to draw the blood.

It took us about 6 months to develop an operating prototype. We decided to try it out by hiring a professional blood donor, bleeding the donor twice a week, and then doing weekly fragility studies plus other blood chemistry to see if there were any ill effects. We managed to find a donor who showed up at the laboratory at the appointed day and hour, but when we explained to him what we intended to do, he looked startled, then frightened, and then picked up his hat and walked out.

Aaronson and I tried to enlist other paid donors with much the same result and finally decided that the only feasible way of testing our prototype was to bleed each other. Dutifully, I would stop at the laboratory on my way home from work each Monday and Friday afternoon, and Dr. Aaronson would bleed me, and then I would bleed him. This went on for about 6 months with no adverse effects on either of us. We then decided it was time to market the product.

We made appointments with the Red Cross, Army, and Navy offices in Washington to demonstrate the product. Carrying along a large box containing substantial quantities of donated whole blood packed in ice (this was 1944, remember), Aaronson and I got on the Congressional Limited Train from New York to Washington. Feeling very pleased with ourselves, we had reserved seats in the club car populated by all the VIPs going to Washington. We plunked down our large box of blood packed in ice and took our seats. Near Philadelphia, we noticed a thin, red stream of blood emanating from the box. Our fellow passengers were too polite to comment, but we were so embarrassed that we pretended the box did not belong to us until we got to Washington. Fortunately, only one of the many bottles that we had taken was broken.

Once in Washington, Aaronson and I dutifully made the round of offices of the Red Cross, Navy, and Army, only to be told in each case that, despite the public appeals, the one thing the military had in abundance was blood plasma! In fact, both the Navy and Army made a point of telling us that the first thing to be jettisoned in times of battle trauma was blood plasma. Thus, our "market" completely disappeared, and we abandoned our project, having spent a considerable amount of effort and received a patent for our efforts.

About 10 years later, a pediatrician in Philadelphia, whose name I believe was Gibbons, was promoting the use of gamma globulin to prevent polio. He had heard of our efforts and invited us to appear first at a medical meeting, and then on a television program depicting the use of gamma globulin to control polio. There was a brief flurry of interest in our device by the research community, but it ended with the success of the Salk vaccine.

In the 1970s, I was flabbergasted to observe what in practice was a replica of our original device, offered for sale by first one and then several other companies. The last time I looked, one firm, Haemonetics, a firm totally devoted to plasmapheresis, had sales of approximately $30 million. Of course, this was more than 30 years after our original work. I am reasonably convinced that the market was not ready for our product. It would be quite a different story today.

VIGNETTE #14
WHEELCHAIRS FOR THE THIRD WORLD

Ralf Hotchkiss
Appropriate Technology for Independent Living
Oakland, California

INTRODUCTION

For the past 20 years, I have been involved in wheelchair design and innovation. I became a paraplegic in 1966 and began by modifying my first chair. Currently, I work full-time on wheelchair design. For the past 12 years, I have been involved in making stair-climbing wheelchairs, stand/squat models, and high-speed sports chairs. My current focus is the design of lightweight folding wheelchairs for manufacture in developing countries.

THE DESIGN CRITERIA

Wheelchairs used in developing countries can run into the same problems as wheelchairs anywhere else. When the chairs are used actively, for example to climb curbs or follow rocky trails, they bend and break if they are not properly reinforced. When they are propelled over rough ground, they lose traction and become impossible to push if they do not have pneumatic tires. If they are any wider than necessary, they will not fit through many doorways; if they are too heavy, they will be hard to push and lift; if they don't fold, they will not fit in the aisle of a bus or on the side of a donkey.

Over the past 45 years since the lightweight folding wheelchair was introduced, experienced wheelchair riders have learned how to specify those features that enable a wheelchair to be used effectively over rough terrain. Many attempts have been made to improve on the wheelchair's function, and active users have adopted some significant refinements. Furthermore, some new types of vehicles, such as hand-powered tricycles, have proved useful for

outdoor transportation, especially for folks with limited walking ability. With rare exceptions, however, full-time users needing a single vehicle for both indoor and outdoor use have found nothing better than four-wheeled, rear-drive wheelchairs.

Other types of wheelchairs have fallen out of favor because they lacked some of the following features:

- o Width: 24 inches maximum for a 16 inch or greater seat width.
- o Length: 42 inches.
- o Weight: 45 pounds for a fully equipped chair with armrest/fenders, brakes, footrests, handrims. Lightweight aluminum folding chairs, weighing as little as 30 pounds fully equipped, are now available at high cost.
- o Traction/Maneuverability: A skilled rider of a four-wheeled, rear-drive chair can easily shift all of his/her weight to the drive wheels, giving full traction over rough terrain. When combined with pneumatic tires and flexible frame, the four-wheeled, rear-drive chair gives excellent propellability and better stability than any other three-wheeler of comparable width.
- o Ease of Assistance: The rear-wheel-drive chair can be tipped back on the rear wheels by an assistant and pushed or pulled over curbs and rough terrain.
- o Folds: To a width of 12 inches or less. Easy disassembly of the chair by the rider has also been accepted by some users.
- o Accessibility: The chair must not interfere with pulling close to a work table or, for users who cannot stand, making lateral transfers into and out of the chair.

- Durability: The chair must stand up to the shock of ramming curbs and chuckholes and withstand rough treatment in all types of transit. It must not be prone to breakdowns, which will strand the rider far from service facilities, and must perform with a minimum of routine maintenance. Commercial chairs vary widely in this regard, with some of the least durable chairs also being the heaviest and most expensive.

If these criteria are important for active wheelchair riders in the Western World, they are triply important for riders in Third World countries where:

- doors are narrower;
- turning spaces are smaller;
- chairs must be lifted more often;
- roads are rougher;
- curbs and steps are larger and less uniform;
- assistance in getting over obstacles will be needed more often; and
- access to repairs is far more restricted.

Thus, our goal became the design of a wheelchair at least as good as the best Western models, but less expensive, made out of locally available materials, and buildable in a workshop set up with an absolute minimum of capital.

WHEELCHAIRS FROM THE WESTERN WORLD

The provision of wheelchairs for developing countries by philanthropic groups from the Western World has been, from the point of view of experienced wheelchair riders, curious though not surprising. In country after country, with few exceptions, the pattern has been the same.

Western "experts," with the best of intentions, have brought low-cost, hospital-style wheelchairs into developing countries and found that these chairs do not move easily over unpaved terrain. Instead of checking with experienced wheelchair riders to find out what types of chairs would be best for rural use, these experts have arrived at the blanket conclusion that "Western style wheelchairs...[are] of quite limited use" (leading organization in the rehabilitation field quoted in the International Rehab Review, 2nd 1/4, 1983). The experts have then proceeded to reinvent chairs which were outmoded, in most cases, by designs patented before the Depression. These chairs have been wider, heavier, had poorer traction, have been harder to assist than top-quality Western wheelchairs, and they haven't been able to be folded.

NICARAGUA WHEELCHAIR PROJECT

In 1980, I was contacted by another disabled man involved with the independent living movement, Bruce Curtis. He had just returned from a trip to Caribbean and Central American countries, including Nicaragua. He was most enthusiastic about a group of disabled people he had met at a rehabilitation center in Managua, many of whom had become disabled during the revolution of 1979. These disabled Nicaraguans needed assistance with wheelchair repairs and wanted to learn to drive with hand controls. More important, they were very interested in the concept of independent living, which had given birth to numerous independent living centers in the United States.

This contact led to my first trip to Nicaragua in 1980. I met many disabled people there and began to assess their problems in obtaining and maintaining wheelchairs that they could afford and which would meet their needs. I found that the disabled Nicaraguans who had managed to get wheelchairs used two types of chairs. The vast majority of people had second- or third-hand hospital-type chairs which had hard tires, nonremovable armrests and footrests, and gave the users little flexibility of use or mobility. Such wheelchairs had frequent breakdowns and were not very useful out of doors.

The second type of chair was a U.S. prescription model, which very few people had because it was very expensive by Nicaraguan standards. This type of chair was easier to use, but gave its riders many of the same problems as the others. It was quite heavy and the seat widths of the standard imported models tended to be far too wide for the Nicaraguans. Many common replacement parts were impossible to get because American wheelchairs aren't made from generic, interchangeable parts.

During my 1980 trip, I also worked with the other disabled people from the United States to provide as much information to the disabled Nicaraguans about independent living as we could. I spent one afternoon with my portable hand controls and a borrowed car giving driving lessons, which turned into a rather reckless but nonetheless worthwhile endeavor. We discussed sexuality, independent living skills, architectural barrier removal, and making social advances in the political arena in small groups. I also gave lessons in wheelchair repair and fixed several chairs in the process.

This visit set into motion the formation of an independent living center organized and run by some of the disabled Nicaraguans from the rehabilitation center. The people involved were given a house by the Nicaraguan Government to use as an office. One of the group's top priorities was to set up a wheelchair repair and manufacturing facility that would address the great need for wheelchair repair and for new wheelchairs that people could afford. The group also wanted to plan for the economic development and eventual self-sufficiency of the independent living center.

U.S. FOUNDATION SUPPORT

After I returned to the United States, I submitted a proposal to a Washington-based group, Appropriate Technology International, for me to provide technical assistance to the Managua independent living center for the establishment of its wheelchair repair and manufacturing shop. This proposal was accepted for a one year contract. I developed a prototype of a Third World appropriate wheelchair at my shop in Oakland, California, and made several trips to Nicaragua to help the independent living center organize its shop, purchase its tools and equipment, develop wheelchair repair and modification techniques, and begin to make wheelchairs.

Under a second contract with Appropriate Technology International, we completed the Nicaragua project and began to spread the wheelchair design and its technology to disabled people and their organizations from the Caribbean, Central America, and South America.

EVOLUTION OF THE DESIGN

The first prototype design for a Third World appropriate technology wheelchair was based on western wheelchairs made for rural use. The design has now gone through several major revisions. During the first year, most of the work on it was mine. After that, one of the disabled Nicaraguans, Omar Talavera, made significant contributions to the design. In 1981 we visited Tahananwalanghagdanan (House with no stairs) in the Philippines. There we met twenty wheelchair riders who had built more than 1,000 low cost chairs. Their critical suggestions led to more changes in our design.

The major problems in developing the original idea into a workable prototype stemmed from the lack of materials and my poor understanding of wheelchair use in Nicaragua. I discovered that it is not enough to know the ins and outs of wheelchair use from a technical and consumer perspective. I came to understand that making and using a wheelchair in the United States and in a developing country are two different things.

The ease with which we can obtain parts in the United States is almost embarrassing. The unavailability of parts in Nicaragua quickly began to dictate the design of our wheelchair. I had already decided to use zinc-plated electrical conduit instead of inch-sized seamed metal tubing because the standard sizes of electrical conduit were more widely available. The prototype design changed as I discovered what else was not available: hardened bolts, concentric tubing sizes, suitable ready-made hubs, and more.

In addition, the economic situation in Nicaragua made it difficult, and sometimes impossible, for the wheelchair shop to purchase custom-made wheelchair parts from outside the country. We were forced to find ways to make most of the wheelchair components out of standard Nicaraguan hardware. We are still trying to work out how to make a high-resiliency, low-cost front wheel, but everything else is made out of locally available materials.

My naivete about the lifestyle of disabled Nicaraguans caused one major prototype change. My original design called for a wooden folding seat, which allowed me to use a simpler and stronger folding mechanism than the mechanism in the average U.S. chair. That design had to be scrapped, forcing a major design modification, however, because I had not taken into consideration the fact that, unlike wheelchair riders in the United States, most Nicaraguan wheelchair-riders do not use wheelchair cushions. A wooden seat would cause decubitus ulcers for people with spinal cord injuries. During the first year, I bought some cushions and tried to convince the group to use them. As the cushions wore out and needed replacement, I finally realized why most Nicaraguans would never use cushions--they can't afford new ones. Also, I had overlooked the need in Nicaragua for a wheelchair folding design that allows the rider to partially fold the chair without getting out of it. The Nicaraguans partially fold their chairs in order to squeeze through the narrow doorways which exist throughout the country. We have enough barrier-free buildings in the United States by now that this is not considered an essential feature.

As a result of these economic and practical problems, the current wheelchair design is almost completely original and is more closely designed to meet the needs of disabled people who live in rural areas and can't afford anything but the cheapest of wheelchairs.

MANAGEMENT OF THE SMALL BUSINESS

The ability of the Managua independent living center to proceed beyond the prototype development and launch into actual marketing of the wheelchairs has been hampered by the problems the country has had in maintaining a general inventory of basic materials. Another problem is that the disabled people who run the independent living center, who grew up in poverty, are not used to the concept of purchasing in bulk. They are used to buying today what they need for today, and as a result, they will sometimes lose an opportunity to buy needed materials when they are available.

MARKETING

The potential market for wheelchairs in Managua is great, if it is measured by the need. However, not many disabled Nicaraguans can afford to buy their own wheelchairs, even though the Managua-made wheelchair is much less costly than foreign imports. A few of the wheelchairs have been purchased by individuals. Wheelchair repairs performed at the independent living center have been paid for by the Nicaraguan Government, and it is hoped that the Government will be able to pay for wheelchairs for some of the people who can't afford them.

PATENT PROTECTION

My policy regarding patents for wheelchair developments is to publish a description of the invention, thus placing it in the public domain. I have seen too many good ideas that have not ended up in the consumers' hands because of seemingly endless disputes between companies and entrepreneurs over patent rights. In the end, most patents are easy enough to modify so that the

basic idea can be used without providing compensation to the patent holder. Thus, I don't believe patents are very valuable to most inventors and certainly not for consumers. At any rate, Nicaragua doesn't have a system of patents, and U.S. patent rights don't apply there. So, for the Nicaragua project, the issue of patents has not been important. The same is true for Food and Drug Administration (FDA) regulations, which of course don't apply outside the United States.

ENGINEERING STANDARDS

The Veterans Administration (VA) wheelchair standards, which may serve as a model for the FDA standards, have been very helpful in designing tests for our Third World wheelchair prototypes. Access to testing equipment such as that used by the VA would also be of considerable help.

A committee of the American National Standards Institute has been established to write wheelchair standards, but nothing has been completed yet.

THE FUTURE...

So far, 50 wheelchairs have been sold to private individuals in Nicaragua. At present, the materials for one chair cost about $80 (U.S.), and 4-5 person-days are needed to complete each chair. The sales price is about $170 (U.S.).

Durability and ruggedness have been major characteristics built into our wheelchair's design, and it is hoped that the wheelchairs can be maintained indefinitely. The maintenance of the wheelchairs will be aided by the fact that Nicaraguans and disabled people in developing countries tend to be quite inventive in their ability to use available materials and find new ways to make old devices last a long time. Some corrosion of the metal parts

of the wheelchair will occur in wheelchairs used near the ocean or salt water lakes, and in these areas, replacements may be needed more frequently. The availability of conduit that has been galvanized both inside and outside the tubing will help solve this problem.

DISSEMINATION

We have begun to spread what we have learned. Under the sponsorship of Appropriate Technology International, we have held workshops in Jamaica, Peru, Costa Rica, Honduras, the U.S, and the Philippines. Wheelchair production is beginning or is underway in twenty locations in twelve countries, and several more will start soon. A 150-page production manual, Independence Through Mobility, is now available from AT International. A new project, Appropriate Technology for Independent Living, has begun in California to carry on the development and dissemination of our wheelchair design worldwide.

VIGNETTE #15
THE DEVELOPMENT OF THE ULTRASONIC HEAD CONTROL UNIT

David Jaffe, M.S.E.
Rehabilitative Engineering Research
and Development Center
Palo Alto VA Medical Center
Palo Alto, California

While it is often said that "necessity is the mother of invention," innovation occurs only in the presence of both technology and opportunity. Technology is the know-how to produce a new device, process, or application of an older technology for a new purpose; and opportunity consists of both human and material resources. The successful mixture of these two elements results in the acquisition of new knowledge or the creation of a new device--either of which may be considered innovations. The opportunity for a manufacturer to increase profits by satisfying a market need plays an important role in catalyzing this process. Graphically, the equation may be represented as:

Need
People
Environment $\geq$ Innovation + $
Technology
Funding

If the devices, knowledge, and profits from innovation can be fed back into the technology and funding factors on the left side of the equation, this equation can become self-sustaining.

In this essay, I will discuss the chronological history of the development of the ultrasonic head control unit (UHCU) in the context of these factors. The UHCU is a powerful new device developed to meet the need for an alternate method of control of wheelchairs and other devices by quadriplegics.

Developed using new technology, Polaroid's commercial ultrasonic sensor system, the UHCU was the product of many years of effort involving many setbacks and detours.

The source of the UHCU project predates my employment with the Veterans Administration (VA) Rehabilitation Research and Development (R&D) Center in 1979. In the 1970s, prior to his association with the VA, Dr. Larry Leifer was personally interested in robotics. Along with Vic Scheinman, he investigated various robotic arm designs. Many of their ideas were incorporated in a series of commercial manipulators now manufactured by Unimation. Substitution of these factors into the equation gives:

Time	1970-1979
Need	Personal interests
People	Larry Leifer
	Vic Scheinman
Environment	National Aeronautics and Space Administration
Technology	Servo controls
	Mechanical engineering control theory
Funding	
$\geq$	
Innovation	Commercial robotic arm system

In 1978, the VA announced the formation of the Rehabilitative Engineering R&D Service as a division of the VA's Medical Research Services. Two VA field centers--at the VA Medical Centers in Hines, Illinois and Palo Alto, California--were mandated to "use state-of-the-art science and technology to benefit disabled individuals."

Larry Leifer, an assistant professor of mechanical engineering at Stanford was appointed Director of the Palo Alto R&D center. Thus, Stanford's Mechanical Engineering Department was affiliated with the VA's Rehabilitative Engineering R&D Center in Palo Alto in much the same manner that Stanford Medical Center is affiliated with the VA Medical Center in Palo Alto. Substitution of these factors into the equation gives:

Time	1978
Need	Ongoing personal interests
People	Larry Leifer VA Central Office
Environment	Stanford University Palo Alto VA Medical Center VA Rehabilitative Engineering R&D Center
Technology	
Funding	

The VA involvement served to focus Dr. Leifer's research interest on the possible practical application of robotics technology for use by disabled individuals. With VA seed money, construction of a rehabilitative engineering R&D facility on the grounds of the Palo Alto VA Medical Center was begun, and the hiring of personnel was initiated.

Prior to the completion of the VA facility in July of 1980, work on the application of robotics proceeded in the Design Division of Stanford's Mechanical Engineering Department. Students in Dr. Leifer's mechanical engineering course entitled "Smart Product Design" explored the use of a Unimation Puma 250 Robotic Arm to accomplish tasks of everyday living. Substitution of these factors into the equation gives:

Time	1979
Need	Meet VA mandate
People	Larry Leifer VA Rehabilitative Engineering R&D Center Consultants Staff Stanford mechanical engineering students
Environment	Stanford University, Mechanical Engineering Department Temporary VA Rehabilitative Engineering R&D Center Office
Technology	Commercial manipulator
Funding	Initial VA funding

The students in Dr. Leifer's "Smart Product Design" course were assigned the task of using a robotic arm to bake a cake. The arm could be commanded either through a robotic programming language or through a remote control box that operated the six motors of the arm with single switches. Use

of the programming language to command the arm required a CRT terminal and knowledge of the robotics language VAL. The programmer could command the computer system of the robotic arm to execute a sequence of instructions. The robotic arm could then perform actions such as pouring batter, but only in a structured environment (e.g., with the containers for the batter placed in the spots the arm expected them to be).

The remote control box allowed the user to control the arm in real-time; that is, the results of the operator's switch activations could be observed and subsequent actions could be taken to command the arm to the successful completion of its task, even in an environment unknown to the robotic arm system. Allowing for a redefinition of "cake" to include "pancake," the robotic arm proved itself to be a fairly capable cook in the right programmer's hands.

Dr. Leifer's students drew two conclusions from their experiment. The first was that a robotic arm could be employed by a disabled user in some tasks of everyday living. The second was that new methods of commanding the arm were desirable, especially if the disabled user had no use of his or her hands or arms. Substitution of these factors into the equation gives:

Time	
Need	Adapt robotic arm for disabled users (project assignment)
People	Stanford mechanical engineering students
Environment	Stanford University, Mechanical Engineering Department, Smart Products Design Laboratory
Technology	Commercial manipulator
Funding	

Dr. Leifer's students investigated input interface devices for disabled individuals and learned that quadriplegic wheelchair control was typically accomplished by a chin-controlled joystick. A chin-controlled joystick could not be directly substituted for the remote control box because its only two motions (backward/forward and left/right) would be insufficient to control all

six motors of the robotic arm. Nevertheless, the use of the chin as a control site for the robotic arm was pursued.

The students' initial attempt at developing a robotic-arm-control device that quadriplegic individuals could manipulate involved chin-activated switches that performed the same function as the switches on the remote control box. The seven switches were arranged horizontally in front of the user and were supported by a short camera tripod.

From the first trial of this device, it was clear that although the device could be used by disabled individuals, it was inefficient and difficult to use since only one switch could be activated at a time to produce a robotic action. A typical task required many such activations, each requiring visual identification of the proper switch and observation of the resultant robot motion in relation to the task goal. Substitution of these factors into the equation gives:

Time	1979
Need	Head control unit for piloting a robotic arm
People	Stanford students: William Shriver, M.S.M.E. Steve Tipton, M.S.M.E. Advisors: Professor Larry Leifer, Ph.D. Professor Philip Barkan, Ph.D. Liaison: Inder Perkash, M.D., VA SCIS Richard Ferdinand, P.T., VA SCIS
Environment	ME 210abc, Graduate Machine Design
Technology	
Funding	

At this point, the flow of the Stanford student project bifurcated: voice control was proposed for the robotic arm and an alternate interface mechanism was sought for quadriplegic wheelchair control.

The students found several problems with the control of electric wheelchairs by quadriplegics. Wheelchairs designed for severely disabled individuals in the past typically have used a mechanical user/device interface such as a chin- or head-controlled joystick. These mechanical interface

devices require direct physical contact with the disabled user and are therefore far from ideal. Furthermore, to accommodate the severely disabled user, such devices have to be carefully positioned. Limited chin extension and marginal control of chin movements aggravate the control problem and prove frustrating for many quadriplegic users. Furthermore, chair motion tends to be quite jerky because of the acceleration feedback effect of the chair on the user's head position. Other interface devices, such as pneumatic puff/sip switches, present similar control problems, are harder for users to master control of, and pose obvious sanitation problems. Moreover, aesthetic factors have been frequently overlooked in the design of wheelchair system for quadriplegics.

Confronted by these problems, a group of five graduate students in the Design Division of Stanford's Mechanical Engineering Department were assigned the task of designing an alternative and innovative control and guidance system for an electric vehicle capable of transporting quadriplegic individuals. The vehicle was specified to be maneuverable in its environment with a minimum of operator input. Additional desirable capabilities for the vehicle included sensing, recognizing, and interpreting the environment. The vehicle was to acquire sensory information by sensing objects ahead of it, avoid collisions with obstacles in its path (such as stationary objects or a suddenly opening door), and maintain its bearing with respect to the walls around it. The vehicle's control system was specified to be operated by the user's head in a manner that did not obstruct vision, limit normal head movements, or interfere with normal activities.

The "Smart Wheelchair" produced by the Stanford students was a microprocessor-based system which sensed its environment using ultrasonic transducers and commanded chair movement. The "Smart Wheelchair" system was

built around a standard Everest & Jennings Model 3P wheelchair, which is normally operated by a joystick. The completed system enabled the chair to operate in any of several modes: training, head control, obstacle detection, wall tracking, cruise control, and stop.

Two Polaroid ultrasonic sensors on a lap board were used to track the position of the user's head, so as to give him or her the ability to navigate the chair solely by head motion. Other sensors performed the other tasks and were mounted facing to the front and to the sides of the wheelchair.

The two Polaroid ultrasonic sensors used to track the "Smart Wheelchair" user's head position emitted inaudible sound waves which moved through the air until reflected by an object. A portion of the echo signal returned to the transmitting sensor and was detected by the associated electronics. The measured time from transmission to the reception of the echo was proportional to twice the distance from the sensor to the object. In its commercial camera application, Polaroid's ultrasonic sensor accomplishes camera focusing by ranging the distance from the camera to the subject being photographed. In the "Smart Wheelchair" application, the two stationary sensors on the lap board and the wheelchair user's moving head describe a triangle, and a geometric relationship allows the offset from the base line and center line of the two sensors to be calculated. This information is then used to map the user's head position into navigation signals for the wheelchair.

By tilting their heads off the vertical axis in the forward/backward or left/right directions, users can make the chair move in the direction of the head tilt at a rate proportional to the magnitude of that tilt, thus emulating the effects that a hand-operated joystick produces with a standard electric wheelchair.

The UHCU interface used in the "Smart Wheelchair" would meet the mobility needs of a majority of severely disabled individuals who have no use of their arms or legs but still retain good head control. Its main advantage is that it requires no mechanical contact between the sensors and user's head. The separation of the user from the device used to control the wheelchair means that users of the UHCU interface shouldn't feel 'wired-up' or confined by devices around their face or body, as they frequently do with other interfaces designed for them. The fact that current implementations of the UHCU on electric wheelchairs draw little public attention suggests that the UHCU is a socially acceptable device.

In operation, the "Smart Wheelchair" with the UHCU performed much as expected; with about an hour's practice, most users were able to master its operation. Some difficulties became evident, however. The rearward movement of the user's head that was required for reverse travel often triggered a mode change sequence normally initiated by an extreme rearward motion. In addition, desired straight line navigation resulted in a zig-zag travel path. This difficulty was traced to a low frequency oversteering instability due to the low ultrasonic data acquisition rate and the poor arithmetic approximations made in the calculation of head position.

Despite its successes, the "Smart Wheelchair" was not a practical vehicle. The method of loading the program from disk was time consuming, and in any case, could not be performed by a disabled user. The disk drives and CRT required a source of alternating current power, which might not be available in places where the chair might travel. The batteries required for computer operation were not rechargeable. The software was difficult to maintain and modify. The lap board on which the sensors were mounted proved to be a barrier to transferring users into and out of the chair.

These problems could not be easily corrected on the existing "Smart Wheelchair." Nevertheless, the chair designed by the Stanford students did prove the merits of computer-controlled mobility directed by head position. The practical execution of these concepts would have to be accomplished in a subsequent design. The equation at this point may be represented as follows:

Time	School Year 1979-1980
Need	ME210 (Graduate Machine Design) project assignment
People	Stanford graduate mechanical engineering students: Karen Altman Rick Epstein Leslie Gerding Wayne Leger Dave Parker Liaisons: Children's Hospital at Stanford Wally Motloch Stanford University Larry Leifer Michel Parent VA Rehabilitative Engineering R&D Center David L. Jaffe
Environment	Stanford University, Mechanical Engineering Department, Design Division, Smart Products Design Laboratory
Technology	Polaroid ultrasonic sensors Microcomputers
Funding	VA student pilot project, $10,000
≥ Innovation	"Smart Wheelchair"

The heart of the "Smart Wheelchair," the UHCU interface, appeared to have utility beyond wheelchair control. Its noncontacting operation was particularly appealing for severely physically disabled individuals who did not have control of their arms or legs but retained good head and neck control. For these reasons, a decision was made to concentrate primarily on developing the interface and investigating its application to a wider range of rehabilitation problems. In July 1981, I submitted a proposal to undertake this work to the Technology and Research Foundation of the Paralyzed Veterans of America. The foundation provided funding, and in May 1982, we began work

on the UHCU project at the VA Rehabilitation R&D Center. The equation here may be represented as follows:

Time	1981
Need	A general and practical implementation of the UHCU interface
People	David L. Jaffe
Environment	VA Rehabilitation R&D Center
Technology	Polaroid ultrasonic sensors Microcomputers
Funding	Paralyzed Veterans of America (Technology and Research Foundation) $17,288

Work under this grant from the Paralyzed Veterans of America focused on the design and development of a new generalized interface, the UHCU, which employed the same ranging scheme as the "Smart Wheelchair." In the most general case, the UHCU can map two degrees of distance information into an alternative control space. In the wheelchair application, for example, the user's head position is translated into navigation signals to the electric motors on the chair; the user merely tilts his head in the direction he wishes the chair to move.

The current version of the UHCU in the electric wheelchair application has overcome many of the problems that plagued the ultrasonic interface on the student-designed "Smart Wheelchair" and is therefore a device that is more practical and marketable. The unit is built with commercially available circuit boards that were designed for process control applications rather than the "Smart Wheelchair's" modified development system. A newly developed software program for the unit accurately calculates the user's head position and executes from nonvolatile memory, thereby eliminating the need to load the code from an external disk drive. When the system power is applied, the program is instantly available. The software includes an automatic calibration sequence and algorithms for filtering and averaging head position information. A press of a switch located behind the user's head activates the

unit, while another stops it. The Polaroid sensor interface has been redesigned to increase the distance ranging acquisition rate and thus eliminates the oversteering tendency of the previous design. These new features make this device completely controllable by a disabled user.

Physically, the UHCU is 5+ inches by 9+ inches by 10 inches in size, weighs approximately 6 pounds, and requires 2+ amperes of 5 volt power. The transducers and head switch are external to the unit and can be mounted 5 feet from it. The multiple types of communication channels can be configured to produce a variety of output modes to accommodate a diversity of controlled devices. In addition, any one of these channels can accept commands from an external computer in order to alter control parameters or operating modes.

The UHCU has been tested in two wheelchair applications: one with an Everest & Jennings 3P wheelchair and the other with a Solo-Power-Pak-equipped Invacare Rolls IV wheelchair. The use of the former device by a quariplegic woman and the demonstration of the other provide evidence that the use of the remote sensing ability of the UHCU will result in rehabilitation devices that are both socially acceptable and aesthetically pleasing. In addition to having wheelchair applications, the UHCU can be directly substituted in other applications were a joystick is currently used--e.g., to control video games, communication boards, and robotic arms.

Currently, the VA Rehabilitation Center is seeking companies to market either the custom Polaroid Interface Board, the UHCU, or its application in wheelchair control. A program of evaluation is under way, as are several additional rehabilitation applications of the UHCU. The market for research devices such as those developed by the VA Rehabilitation R&D Center is commercial manufacturers and not end users directly. Commercial manufacturers, of course, want to be assured that they can sell such devices

to end users and be able to make a profit. For that reason, an initial needs determination is performed prior to committing resources to a specific project. The response from public presentations and consultations with experts in the field serve as a barometer of the validity and need for devices under development.

The responsibility of the VA Rehabilitation R&D Center in the process of innovation includes the identification, design, development, and evaluation of new devices, as well as the marketing of the concept and the transfer of the acquired technology. Product marketing is one of the concerns of companies wishing to use technology in saleable new products. Although the separation of the design/development and production phases can be a barrier to diffusion of research ideas into the marketplace, early involvement and interest of manufacturers can help overcome it.

The UHCU was the first device of the VA Rehabilitation R&D Center for which a patent application through the VA was pursued. The critical 1-year time period elapsed without a patent being granted, primarily due to unfamiliarity with the process.

The tax exempt status of the VA facilitated donations from private industry. The rehabilitation nature of the UHCU device also helped in obtaining some contributions of hardware and software, as did the liaison with Stanford.

In developing the UHCU, the requirements of the Food and Drug Administration were never considered. The VA standards for wheelchairs were considered since veterans would be likely users of the UHCU. As standards for wheelchair controllers continue to be developed, compliance with those standards will become important during all research phases of the project.

The final equation for the innovations described in this essay can be written as follows:

Time	1970-1983
Need	Alternative man/machine interface for disabled individuals
People	Stanford University: Mechanical engineering students Mechanical Engineering Department, Design Division Faculty Advisors VA VA Central Office Palo Alto VA Medical Center VA Rehabilitation R&D Center Supporters: Paralyzed Veterans of America Polaroid Jib Ray Intel Invacare Solo Products Vector Electric
Environment	Stanford University ME210 Smart Products Design Laboratory VA Rehabilitation R&D Center
Technology	Microcomputers Forth Polaroid ultrasonic sensors
Funding	VA Paralyzed Veterans of America
$\geq$	
Innovation	Ultrasonic head control unit (UHCU) Wheelchair applications of UHCU Other applications of UHCU

In summary, I believe the following factors contributed to the UHCU project's success:

- o Individuals with a continuing personal research interest.
- o Direction for ideas--a goal which is driven by need.
- o Infusion of funding at several times during the four stages of the UHCU project: conception, proof-of-concept, development, and the marketing/technology transfer. The successful completion of each phase was assured by adequate support.

- Local private support of hardware, software, and materials. The project was able to solicit support from local Silicon Valley industries.
- Student environment in which to prove the fundamental concept and produce first prototype device in a relatively short time with a minimum of expenditure.
- Availability of the technology required to implement the idea.
- Publicity that generated both public and market interest and feedback for the researchers.
- Acquisition of information about new technology that was required to employ the technology in a new design.

VIGNETTE #16
THE DEVELOPMENT OF AN ARTIFICIAL SPHINCTER FOR OSTOMY PATIENTS

Reed B. Harker
University of Michigan
Ann Arbor, Michigan

INTRODUCTION

For a large number of patients with intestinal cancer, blockage of the intestine, perforations, etc., the only effective treatment today is surgery known as ostomy. In a substantial number of patients, the diseased portion of the patient's intestine is removed and the healthy portion is surgically attached to a stoma (opening) in the abdominal wall. After surgery, the contents of the bowel are discharged through the stoma into a bag attached to the patient's outer abdomen. The bag is drained periodically or disposed of and replaced. (Other systems used to collect body secretions or control the flow of internal effluents do exist, but a bag system is the most commonly used.) It is estimated that there are currently 1,250,000 patients who have had this type of surgery, and there are 50,000 new operations performed each year.

Although most ileostomy and colostomy patients may enjoy excellent physical health and live near normal lives, ostomy may directly or indirectly result in both psychological and physical problems that encroach on their quality of life. In most cases, the surgery requires that internal effluents be collected and stored in a bag outside the body. Thus, many patients are concerned about soiling themselves from bag leakage. Because patients do not have absolute control over the flow of effluents into the bag, they may be embarrassed when the flow occurs during social engagements. All of these problems contribute to the mental anxiety of the patient.

Physical problems are associated with attaching the bag and preventing skin irritation. A common method of bag attachment is by means of a connector that surrounds the stoma and is held in place by adhesive. The connector is replaced every few days by peeling off the appliance and attaching a new fixture with clean adhesive. Skin problems that are difficult to manage and sometimes disabling often result. Infection and irritation require immediate attention and may prevent reinstallation of the bag. Care of the stoma involves washing and cleaning it, and inspecting it for change in appearance. Because of unpredictable flows and unsatisfactory stoma management, proper care is difficult to accomplish.

This essay discusses the origin and development by the University of Utah Research Institute (UURI) of a surgically implantable artificial sphincter which may ameliorate some of these problems. The genius of the device, which has yet to be patented or approved by the Food and Drug Administration (FDA), lies in the extreme simplicity of its engineering design.

The device consists of two lightweight rings about 1 inch apart which are held in position by a light support structure. The rings are connected by flexible pressure distribution cords that form a small orifice as the rings are rotated in opposite directions. When the rings are installed around the intestine and rotated, the flexible cords gently compress the intestine and form an effective sphincter. The ostomy patient controls the motion of the rings through the skin of his or her abdomen and thus gains control over the stoma effluent. Yet, because of the flexible nature of the cords, gas pressure is released as in the normal sphincter.

The unique design of the artificial sphincter--which involves the application of pressure distribution cords to the compression system applied to the intestine--is considered very innovative. A single compression source, acting in an uninterrupted fashion, could result in the closing of blood vessels in the intestinal wall, resulting in tissue death. With a system of cords acting in parallel and longitudinally over a section of the intestine, however, the pressure forces are distributed over a relatively large surface, and there is no interruption of blood flow.

The artificial sphincter is lightweight, comfortable, easy to control, and can be used in conjunction with a bag system or, in appropriate cases and with a different control system, can be arranged in the lower abdomen for normal discharge through the anal region. Manufacture of the device will not be complicated because the majority of the parts can be injection-molded and designed so they can be assembled by relatively unskilled labor.

ORIGIN

In 1979, UURI was developing a program in the cause and prevention of cancer in families with heritable colon cancer. The study required the participation and collaboration of colorectal surgeons in Salt Lake City, one of whom was Dr. J. Preston Hughes. Dr. Hughes had a great concern for the problems faced by his ileostomy and colostomy patients because of their lack of control over their intestinal body secretions; and having developed a working relationship with UURI as a result of the colon cancer project, he asked Charles D. Baker, Manager of UURI Engineering Design and Fabrication, if there were a way of developing an artificial sphincter.

Charles Baker undertook the design and testing of the artificial sphincter as part of his employment at UURI. UURI is a not-for-profit corporation owned by the University of Utah with the purpose of transferring technology from the basic science laboratory to the marketplace. One of UURI's divisions, the Utah Biomedical Test Laboratory, has been engaged in applied research and development in the field of medical devices for the past 13 years. Much of its support has come from the National Institutes of Health (NIH) and FDA.

INITIAL EXPERIMENTS

Access to technical information in developing the first prototype was not a problem. The primary sources of information were J. Preston Hughes, M.D. (the physician), Charles D. Baker (the engineer), and the medical literature. A complete literature search was done at the University of Utah College of Medicine to document the problems of ostomy patients. Facilities, equipment, operating rooms, animals, and surgical equipment were all available at UURI.

The first workable prototype of an implantable artificial sphincter was developed after several months of effort and many design changes by the UURI engineer Charles Baker. In the development of a conceptual model, there was very little funding available. The surgical time and much of the engineering time was donated in off hours. Surgical facilities, surgical supplies, machine shop, and engineering supplies were furnished by UURI. However, there were no major expenditures in any area. The largest expense, taken from UURI discretionary funds, was legal fees for patent application. A patent was applied for in January of 1981.

This prototype was used in a 48-hour animal experiment. The experiment should no necrosis of tissue and was deemed a success.

There were no new technologies, as such, invented to enable the development of the artificial sphincter. However, breakthroughs in the development of tissue-compatible materials in recent years had made the implantation of materials in sensitive areas of the body a matter of routine rather than an experimental problem. UURI had done extensive testing of implantable materials as part of a contract to the National Heart, Lung, and Blood Institute. As a result of having gained experience in handling implantable materials, UURI was in a position to deal with problems of implants that for other corporations might have been much more formidable.

The success of the first animal experiment of the artificial sphincter and a market survey by the California Ostomy Society were the basis of the decision to proceed with the development of this device. 50,000 operations were performed per year and the population of patients already having had the surgery numbered 1,250,000. Furthermore, there were indications that many of these 1,250,000 individuals would be willing to undergo a second surgical procedure if a workable artificial sphincter were available. Having considered the size of the market, the next step was to examine the competition. We found there were virtually no other artificial sphincters available on the market. In short, the market was of good size, and there were no competitors.

ENGINEERING DEVELOPMENT AND ANIMAL AND CLINICAL TRIALS

The funds for the initial experiments at UURI represent only a small fraction of the total funding required to develop the artificial sphincter to the stage where it can be marketed.

There are several technical problems with the device that remain to be resolved. Operability of the closing mechanism of the artificial sphincter over short- and long-term periods has yet to be verified in animal experiments. Short-term (1-week) animal tests will be required to demonstrate that the sphincter can be opened and closed through the skin, that it produces little discomfort to the patient, does not cause any dysfunction of the intestinal tract, does not cause infection when properly implanted, controls bowel movements of a patient, and in all respects meets the design requirements.

Much longer animal experiments will be required to ensure that there are no problems associated with the implantation into living tissue of the prosthetic materials used in the sphincter--that is, to demonstrate compatibility. Compatibility is the acceptance of foreign material by living tissue. Where compatibility exists, there is very little tissue growth around the material. Where there is incompatibility, there is a tendency for tissue to grow around the material. In some cases, the growth of tissue is so extensive that it takes on the appearance of a tumor. Such growth would inhibit the operation of the sphincter by restricting the relative movement of the sphincter rings. The problem of incompatibility can be solved through proper selection of materials. Materials for prosthetic devices have been under development for a period of 20 years, and very acceptable materials are now available on the open market. The testing of materials to demonstrate tissue and materials compatibility can be completed in a 6-month animal experiment.

Unwanted tissue growth could also occur as a result of irritation. Callouses on the palm of one's hand are an illustration of tissue growth caused by irritation. In the case of the artificial sphincter, irritation

could result from daily opening and closing of the device or from the constant squeezing of the intestine by the cord material. However, irritation of the intestinal wall should be minimized because the implantable sphincter does not require relative motion between the sphincter cords and the intestinal wall. Preliminary engineering tests will help verify this assumption. Engineering tests will also be used to determine what the optimal force must be to close the intestine, thus reducing irritation to a minimum. Most of the time, minimal pressure will be sufficient. In natural sphincters, maximum strength is required only once or twice each day. This pattern must be copied in the artificial model. Again, animal tests of 6 months' duration will reveal whether or not irritation is a significant problem.

Some tissue-covering of the cords would be desirable because it could make the material look like body tissue. It could also bind the cords in a fixed position on the intestine and provide a cushion on which the cords could press. Artificial heart valves already use such tissue growth to improve their function by sealing action. Tissue is encouraged to grow into certain parts of the valve because it provides a natural seal around the valve and also provides a proper interface between the body and the implanted material. This growth, however, is desirable only to a point. Once the implanted material is covered, all further growth should be inhibited. Inhibition of growth normally occurs in artificial heart valves and can probably be similarly controlled in the artificial sphincter.

These short- and long-term problems are viewed as the main technical questions yet to be resolved. It is envisioned that this animal testing program may take as long as 1 year to clearly demonstrate that proper solutions have been attained.

The next area of testing will be in humans, and a testing program in 40 patients will be required to demonstrate to FDA that the artificial sphincter is safely and effectively doing that which it was designed to do. It will probably take an additional year to properly test the device in humans.

Funding for engineering development and animal and clinical testing of the device--estimated to exceed $2 million--was not available at UURI. To find this funding, UURI turned to several sources. It took 3 years to accomplish its funding objectives.

One source to which UURI turned was the Federal Government. Grant applications were submitted to NIH through the usual grant mechanism; all were rejected by the review committees as being outside the research interests of NIH.

As a not-for-profit corporation, UURI was ineligible for Small Business Innovation Research (SBIR) grants through NIH. However, a $50,000 SBIR grant submitted through a private corporation is reported to have been funded. This Phase I grant, to evaluate technical and commercial feasibility of the device, has not yet been awarded. Phase II funding, if granted, will provide an additional $500,000.

The SBIR program is a step-by-step plan to help small businesses in the development of new products. Because of the required review cycle, however, the Federal funding process has been very slow and, though helpful, would take far too long to be practical if there were no other sources of funds.

A second source to which UURI turned for funds was venture capital and industry. Companies contacted included the following:

Idanta Partners - San Diego, California

Steiner Corp. - Salt Lake City, Utah

Mitsubishi - Japan

CW Ventures - New York, New York

Arthur D. Little Investments - Cambridge, Massachusetts

Camelback Investments - Phoenix, Arizona

Capital Investments - Salt Lake City, Utah

IBM - Mt. Kisco, New York

Hollister Corp. - Chicago, Illinois

Smith Kline Beckman - Philadelphia, Pennsylvania

Basically, the companies' response was that until the animal trials of the sphincter were completed, the financial risk was too great.

Furthermore, some investors were reluctant to invest in the product because it was not protected by a patent. The patent for the artificial sphincter had not yet been issued. It is common knowledge that a large corporation can infringe on a patent and a small company can do nothing about it because of the cost of litigation. Hence, a patent has very little value in protecting proprietary rights. On the other hand, a patent seems to provide some level of assurance for an investor, and lack of any patent protection seems to present an unacceptable risk to most investors. Ironically, therefore, there are virtually no outside funds available to help an inventor take an invention from an idea to the patent stage. In the case of the artificial sphincter, UURI channeled the funds from other projects.

Major funding for engineering development and animal and clinical testing of the artificial sphincter was finally obtained through the use of an R&D limited partnership. In a sense, therefore, the Federal tax policies for R&D limited partnerships made the financing of this project possible.

A major stumbling block to obtaining funding was the preparation of a business plan. None of the investors understood the composition of a business plan. Without a plan, financing was not available. It took 6 months to put together an acceptable business plan, which was presented to a number of venture capital organizations. Four of the organizations were willing to invest in the R&D; however, they wanted full development rights in exchange for a few thousand R&D dollars. This was an unsatisfactory arrangement for UURI because it meant no long-term return and no long-term stability for the project.

With the R&D limited partnership, a full $2,083,000 was raised to take the artificial sphincter through all the phases of development, and all of the money was to be spent at UURI. This partnership arrangement was exactly what was needed. By September 27, 1983, the entire $2,083,000 was made available. The plan calls for $1 million to be spent in the first year developing an acceptable implant (which, by definition, is one that will work satisfactorily in 50 animals). After that, human implants will be studied for 1 year before the product can be considered ready for market.

EFFECT OF FDA REGULATORY REQUIREMENTS

The 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act and subsequent FDA regulations require a new implantable device such as the artificial sphincter to undergo a series of tests prior to marketing to demonstrate safety and efficacy. In the worst case, the artificial sphincter could perforate a patient's intestine, possibly resulting in the patient's death. Because of this potential, the artificial sphincter would be classified by FDA as life-threatening, or Class III, the category which requires the most stringent developmental testing as part of FDA's premarket approval process.

To ensure quality research, FDA has what are called Good Laboratory Practices regulations. Moreover, FDA conducts regular inspections of facilities to ensure compliance with these regulations. These laboratory practices would be followed by UURI even if they were not required by FDA. FDA has formalized the requirements and makes UURI's job easier.

To enable FDA to make a proper decision with respect to the safety and efficacy of a device, the sponsor's application for premarket approval by FDA must include certain types of test data. The 1976 law governing device regulation contains a provision on "product development protocol" under which FDA is supposed to help device sponsors in designing their research protocols. If FDA approves the product development protocol, the sponsor's testing program must comply with the plan in all respects. Once the testing program has been completed, the sponsor submits the resulting data and observations to FDA for review. FDA then has 180 days to approve or disapprove the sponsor's premarket approval application.

UURI will approach FDA with preliminary animal test results and a product development protocol for preclinical and clinical trials of the artificial sphincter just as soon as the preliminary data are available. We intend to prepare well for FDA so that expensive rework does not become necessary. By keeping FDA informed of our progress, we hope to avoid delays in marketing the product once the test phase is complete.

FDA maintains strict control over products after they have been marketed. Manufacturing is controlled by FDA's Good Manufacturing Practices regulations, which require standardization and reproducibility of the product. These regulations also require a full quality assurance program with documentation and change control. To meet the intent of these regulations, a complete change control system will be imposed during the manufacturing of the

sphincter. Changes in the sphincter by fabrication personnel and design engineers will not be permitted unless feedback from physicians and patients require them. Even then, changes will be controlled by a review board.

FDA also requires that a registry of implants be maintained listing the implant, the patient, the surgeon, the hospital, the date of implant, etc. The purpose is to maintain traceability. In the event of problems, the physician and patient must be notified of the problem and corrective action to be taken. It is planned that such a traceability program be developed early in the life of the artificial sphincter project.

Securing outside capital for the development of the artificial sphincter, though independent of FDA regulations, has probably been made easier by the existence of FDA regulations. Animal testing and clinical trials are expensive, and, though they would be required with or without the regulations, it was easier to convince investors of the necessity to do the work by saying that FDA required it.

There are some costs associated with preparing the documentation for FDA submissions. In the absence of FDA requirements, however, such documentation would be required in order to make the product marketable. Hospitals and physicians would require proof of adequate testing before the sphincter could be used in patients. Moreover, product liability law suits would require a complete history of the development of the product to ensure that all reasonable and prudent research had been conducted. Hence, I see no added costs due to FDA requirements. If anything, FDA regulations may save costs in the long run.

The existence of FDA regulations may result in more attention being given to the design of the device than might otherwise be the case. However, there are no specific design characteristics of the artificial sphincter which can be attributed to FDA regulations.

MARKETING

The market survey conducted with the Ostomy Society of California indicated a market size of 50,000 patients per year. A second step was to talk with ostomy patients and see if they would be willing to have a sphincter implanted in their abdomen. Most said they would undergo a second operation to gain control over their intestinal discharge.

Since UURI has no marketing arm, contact was made with corporations selling ostomy appliances to see if they would be willing to market the artificial sphincter. All of the corporations contacted have been eager to cooperate. Hence, our plan is to distribute the product through other corporations. Actual experience in sales are at least 2 years away. There will undoubtedly be other procedures developed for colorectal surgery, and there may be other inventions which appear on the market. How long the artificial sphincter will be the only product available is difficult to predict. UURI estimates 10 years.

Reimbursements through Medicare/Medicaid and purchases by the Veterans Administration will be important, but not the main source of revenue. Many ostomy patients are not of Medicare age at the time of surgery. Hence, most reimbursements will come through health insurance or direct payments from younger patients.

Foreign markets may account for 25 percent of sales. Foreign markets may be influenced by the availability of other products such as a magnetic plug for ostomy patients which has some acceptance in Europe. A second influence on foreign markets may be the estimated cost of the surgery and appliance.

VIGNETTE #17
DISPOSABLE SURGICAL PROCEDURE TRAYS

William M. Adams
Health West Marketing
Surgilite International
Long Beach, California

INTRODUCTION

My paper will deal with a new service that is now becoming increasingly popular in surgical facilities. The service essentially involves combining the multitude of individual disposable products that are used daily in high-frequency surgical procedures into customized surgical consolidated procedure trays and supplying the trays to hospitals.

As an independent manufacturer's representative, I am primarily involved with the marketing aspects of the sterile procedure trays and will emphasize these in my paper. I will also discuss the origin and development of the service in order to provide as comprehensive an overview as possible, albeit the information provided is selective commensurate with my knowledge in these areas.

DESCRIPTION

In the medical-surgical disposable products market, customized sterile procedure trays are a relatively new phenomenon. The theory underlying the tray service is actually quite simple: Identify the disposable items--gauze, needles, syringes, suture, tubing, gowns, drapes, gloves scalpels, etc.--which are common to a specific, frequently performed surgical procedure and combine them into a single presterilized procedure tray. The ramifications of using this alternative system of product management are truly dramatic. To appreciate why, we must examine hospital product management procedures.

Most hospitals maintain a totally unitized standing inventory of disposable medical-surgical products for use on a variety of high-frequency "routine" surgical procedures (e.g., coronary bypass, craniotomy, laparoscopy, orthopedic procedures, and cardiac catheterization). The daily maintenance involved with these disposable products is extremely labor intensive, involving a constant cycle of product flow which I have charted in figure 17-1. All of this repetition of labor is geared toward getting the individual disposable products into the proper department in a "ready-to-use" state (i.e., out of the packaging and positioned properly on a sterile area) and the subsequent accounting of these individual products for recordkeeping purposes. Most of this work is performed by talented nurses or technicians whose time is expensive and obviously better utilized elsewhere. Labor accounts for nearly 60 percent of total hospital cost. It is obvious, therefore, that the cost-effective hospital will be one that maximizes utilization of labor and eliminates unnecessary tasks. Consolidating the multitude of disposable supply items used in selected surgical procedures (10 to 200 items per procedure) provides the hospital with some very significant benefits. The benefits include:

- reduced labor cost,
- improved inventory control,
- reduced accounting cost,
- reduced inventory waste/shrinkage,
- reduced operating suite setup and turnaround time,
- improved quality of care, and
- identification of cost on a procedural basis for compliance with regulations under Medicare's new hospital payment system based on diagnosis-related groups (DRGs).

I discuss these benefits further in the marketing section below.

ORIGIN AND DEVELOPMENT

The idea of customizing trays for a specific surgical procedures is not a new one. Customized trays have been prepared, on a limited basis, by various departments within hospitals for many years. A good example is the extensive reusable instrumentation trays which are sterilized, maintained, and processed internally on a daily basis. The degree to which the surgical facility could manipulate presterilized disposable items, however, has been limited.

A problem for hospitals that are trying to increase their efficiency by consolidating disposable items into procedure trays internally is that the party that assumes responsibility for an item's sterility also assumes the liability inherent with that responsibility. The commercialization of the customized tray service by the private sector will allow hospitals to realize the numerous benefits of custom procedure trays without such liability and ultimately much more cost effectively than if the hospitals were to perform the service themselves.

Because the tray concept is in fact a custom service, there was no initial prototype to be developed or complicated patented processes to go through. The technical expertise was readily available in the market. The successful companies are basically just extremely operationally complex kit-packers. The extensive variety and quantity of inventory levels necessary to maintain good service and quality of personnel required to operate the company make the provision of customized trays a fairly capital-intensive business from a startup standpoint. The money for the company I represent, was raised from a group of 120 private investors, 45 of whom happen to be surgeons.

Because we are dealing with sterile product and because the method of sterilization is ethylene oxide gas, we have regular interaction with the Food and Drug Administration and occasional interaction with the Occupational

Safety and Health Administration and the Environmental Protection Agency (for gasses vented from the sterilizer). The following excerpt from our Quality Assurance (Q.A.) Program details the documentation necessary for compliance with Federal regulatory agencies:

> Quality assurance must be a continual effort on the part of all production employees. Controls are maintained throughout the production process, including inspection of all components, packaging, and labeling. Each tray has a device master record which includes specifications for component stock numbers, assembly instructions, and sterilization procedures. Records are maintained for each lot of trays produced, including production, inspection, and sterilization reports. All reports are reviewed by the Q.A. Manager prior to release of the finished product. No tray is shipped without a written release by the Q.A. Manager verifying that all records are complete and that the report of sterility has been received from the lab. A minimum of seven days' quarantine is required to assure ethylene oxide dissipation and to obtain sterility test results.

MARKETING

Custom sterile procedure trays, by definition, are different for every procedure in every hospital. Because they are built to accommodate the brand preference of the user on each individual component, every tray is in fact a new product. This is why sales and marketing play such a critical role in getting procedure trays into the surgical institutions.

A sales representative does not have any physical product when he or she walks in the door, and, more importantly, getting non-business-oriented hospital staff (technicians, nursing supervisors, purchasing agents) to think in terms of cost effectiveness, increased productivity between departments, etc., requires a great deal of interaction. Such terms are not nearly as familiar to the hospital staff as one might assume. With several decades of retrospective reimbursement by Medicare and other third-party payers to cover their budgets, it is understandable why these are sometimes new areas for many

medical professionals.

The rates of acceptance and growth in the market for the customized tray service have been truly impressive, attracting an ever growing network of suppliers and users. Sterile Concepts had over 100 hospitals as customers in its first 2 years in the market. The tremendous rate of acceptance for the service is directly related to what the service yields in benefits to users. Customized procedure trays are an idea whose time seems to have come. In the evolution of disposable products, they are the next most viable extension. This is important when one realizes one is dealing with a market that for the most part was utilizing reusable products in the not so distant past. The reprocessing time involved in utilizing reusable products obviously required saturation of labor.

Marketing customized procedure trays basically involves nothing more than detailing the advantages and the cost effectiveness of the service to the hospital staff and soliciting an evaluation order. However, this task generally takes from 4 months to 1 year per hospital, depending on the number of procedures and level of complexity involved. In hospitals, as in any structures that are bureaucratic in nature, change is generally slow. Although reaction to the service is always very positive, many people have trouble accepting changes too rapidly, and some, as we all know, resist for the sake of resistance.

The principal advantages of customized sterile procedure trays, which I outlined briefly above, are discussed in detail below.

Reduced Labor Cost: Figure 17-1 shows the normal flow of disposable products for the average surgical institution. There are, of course, various adaptations and modifications of hospitals' internal distribution patterns, but generally speaking, regardless of method of internal disbursement, most

products pass through a cycle very similar to the process shown in figure 17-1. The process is extremely labor-intensive, requiring a great deal of duplication of effort and literally thousands of person-hours of labor cost per month.

By combining the disposable items into preassembled trays, one is significantly affecting the labor involved at every junction on the supply flow chart. The most labor-intensive area is the operating room, where setup time for open-heart surgery (pulling supply, aseptically opening the packages, and presenting the individual disposable products) can be as long as 1 hour per procedure. Compound this by 75 to 100 heart procedures per month and you begin to get an idea of the potential time savings available to most hospitals by even partially using preassembled procedure trays.

The use of sterile procedure trays to complement an institution's regular method of disbursement will generally not allow a hospital to make immediate staff reductions. Very few remedies (and certainly no pleasant ones) offer that type of immediate result. Rather, the idea of utilizing the trays is to eliminate unnecessary repetitive manual tasks in order to provide opportunities for the facility: 1) to reduce the need to add staff as the work load increases; 2) to eliminate labor selectively as people retire, transfer, etc.; and 3) to improve the quality of care by redirecting existing labor to more patient-related work.

It is the responsibility of the individual institutions to determine how far they can take these changes. As more business-oriented administrators assume positions of responsibility within the existing hospital framework, the changes seem to come more rapidly.

Improved Inventory Control: Dick Ambrose, Vice President and Chief Materials Manager for National Medical Enterprises, one of the largest privately owned chains of hospitals in the country, estimated in a recent trade journal that 35 percent of his entire supplies budget was in the operating room. He also estimated that this inventory was turning only three to four times a year.

There are many reasons for this situation, not the least of which is the critical nature of most supplies for routine surgeries. In an effort to keep adequate stock levels on hand, many institutions have a tendency to drown themselves in "extra" inventory. In the hospital, as in any type of business, space costs money. Logically, items require much more space when treated individually than they do when consolidated.

Thus, sterile procedure trays allow a hospital to reduce its dollar investment in medical-surgical supplies while assuring that stock levels are adequate to treat both normal situations and any emergencies that might arise. Less space is required throughout the hospital's system. This is important as some operating room areas offer extremely limited storage capabilities.

One other point must be made with respect to inventory control and custom procedure trays. Implementation and utilization of this service encourages a certain amount of inertia toward specific brand standardization for products. The more a hospital can concentrate its volumes into single source brand agreements, the more cost effectively the hospital can purchase.

Many sterile procedure trays are designed as "general" trays to allow various surgeons practicing the same specialty (orthopedics, obstetrics, coronaries, etc.) to benefit from the service. A certain amount of agreement is required if the trays are to be designed as comprehensively as possible (i.e., the more items that go into the trays, the fewer items that must be

treated individually). Utilization of the service facilitates product standardization by focusing attention on duplication of products purchased from different manufacturers.

Reduced Accounting Cost: The consolidation of a large number of surgical supply items into one tray commensurately reduces the accounting charges that such items treated individually incur as they travel their normal path of distribution throughout the hospital (see figure 17-1).

In the operating room, what are normally considered "lost" charges (charges for products that could not be billed to the patient) can be recovered when the items are consolidated. For billing and recordkeeping purposes, literally hundreds of items that are normally treated individually could be consolidated into two or three basic procedure trays. A single tray generates a single charge. By extrapolating the possibilities inherent in designing 13 or 14 general trays (as many hospitals are currently doing), one begins to get an idea of the efficiencies that could be introduced into a system which is badly in need of being streamlined.

Another important point involves the daily massaging of the accounting-recordkeeping system to make adjustments for such routine occurrences as credits/debits for misbillings, picking errors, ordering errors, etc. Other factors are rebilling charges (each error frequently generates another separate exchange of paper work, often for items of insignificant value) and running out of stock.

Obviously, the possibility of running out of an item at a critical time increases proportionately with the number of products one is handling. Running out of a needed item frequently necessitates "emergency" shipments, which are generally billed at a premium charge to the hospital.

In view of the above, I would also reemphasize the importance of the labor which is involved in product maintenance by many people who never see or use the actual products. It is a very hard cost to quantify, and we generally do not attempt to. Nonetheless, it is certainly a cost of doing business to any active surgical facility and should not be ignored.

Reduced Inventory Waste/Shrinkage: Because our company assumes, by virtue of our responsibility for final sterilization of products, the liabilities of the source manufacturers for the various components, we are free to reprocess trays in procedures which are cancelled.

Many times, a questionable reaction to anesthesia or anything that causes a sterile area to be compromised requires a hospital to discard all disposable products in the questionable environment. Cancellation of just a few procedures can result in the disposal by a hospital of literally thousands of dollars in unused supplies monthly. I should point out that this immediate disposal of compromised products by the hospital is done in order to comply with regulations of the Joint Commission on Accreditation of Hospitals.

The reprocessing agreement has been very instrumental in helping to secure accounts as it is readily identifiable as a significant, quantitative savings. Waste, in any industry, is difficult to justify. Prior to the introduction of sterile trays, hospitals justified their waste by the fact that it was mandatory. This argument, to a certain extent, will become much harder to accept as our product life cycle matures.

Reduced Operating Suite Setup and Turnaround Time: Obviously, reduced operating suite setup and turnaround time would be another result of the efficiencies the procedure tray system would induce. I mention it for two reasons. First, most operating room professionals will estimate that it can cost in excess of $600 per hour to run an operating suite; thus, if a

preassembled procedure tray could eliminate even 10 to 15 minutes of operating room time per procedure, the potential dollar savings would be very substantial. Second, many surgeries themselves are not very time consuming once the operating suite has been prepared. For certain types of operations (cataract, retina, ear, nose, throat, etc.), if a facility is saving time before each procedure, it will be able to perform more procedures without increasing the facility or staff requirements.

This benefit is important as a marketing tool, as the sales representative is selling increased effectiveness not only in the utilization of labor but also in the utilization of the institution's facilities. When one considers the dollars that must be generated to recover the cost of the average surgical facility, one can see the necessity for such cost-effective innovations.

Improved Quality of Care: Putting cost effectiveness aside for the moment, I would like to examine another of the benefits derived from a tray program. Eliminating the opening of multiple items in the operating room reduces the risk of potential contamination (i.e., sterile technique is dramatically improved). I am not familiar with any formula that can be used to compute the cost of infection.

Furthermore, utilization of custom trays allows nurses to react swiftly to an emergency or work more effectively during the routine short-staff occurrences that can happen weekly in large institutions. Training time per procedure is reduced; some of the most mundane, repetitive tasks are removed from a long list of daily responsibilities. It is not surprising that the people who actually use the trays like them the most.

Diagnosis Related Groups: Medicare's new prospective hospital payment policies based on DRGs has been instrumental in expediting the growth of our service. The realities of operating a facility under a prospective payment system are just beginning to permeate the institutions.

The recent changes in third-party payment policies have forced the hospital industry to take a long hard look at ways to reduce the escalating cost of providing quality health care. The ability to identify and contain costs will be vital to the survival of hospitals during the 1980s.

Because they are built to accommodate a particular procedure, sterile trays assist in the identification of materials cost on a case-by-case basis. Such identification is essential if a hospital is trying to assess its viability for DRG compliance on a particular surgery. Obviously, the cost-saving ramifications of the trays are more important today than ever before. Sterile procedure trays are, without a doubt, the most innovative solution to the cost of managing disposable medical-surgical supplies.

SUMMARY

The crux of the marketing plan for customized sterile procedure trays is geared toward getting the appropriate decisionmakers to weigh the total cost of product management against the acquisition cost of the individual components that might comprise a particular tray. As the educational process within the hospital industry continues and pressures for cost containment continue to mount from all sides, our service should realize fantastic growth over the rest of the decade.

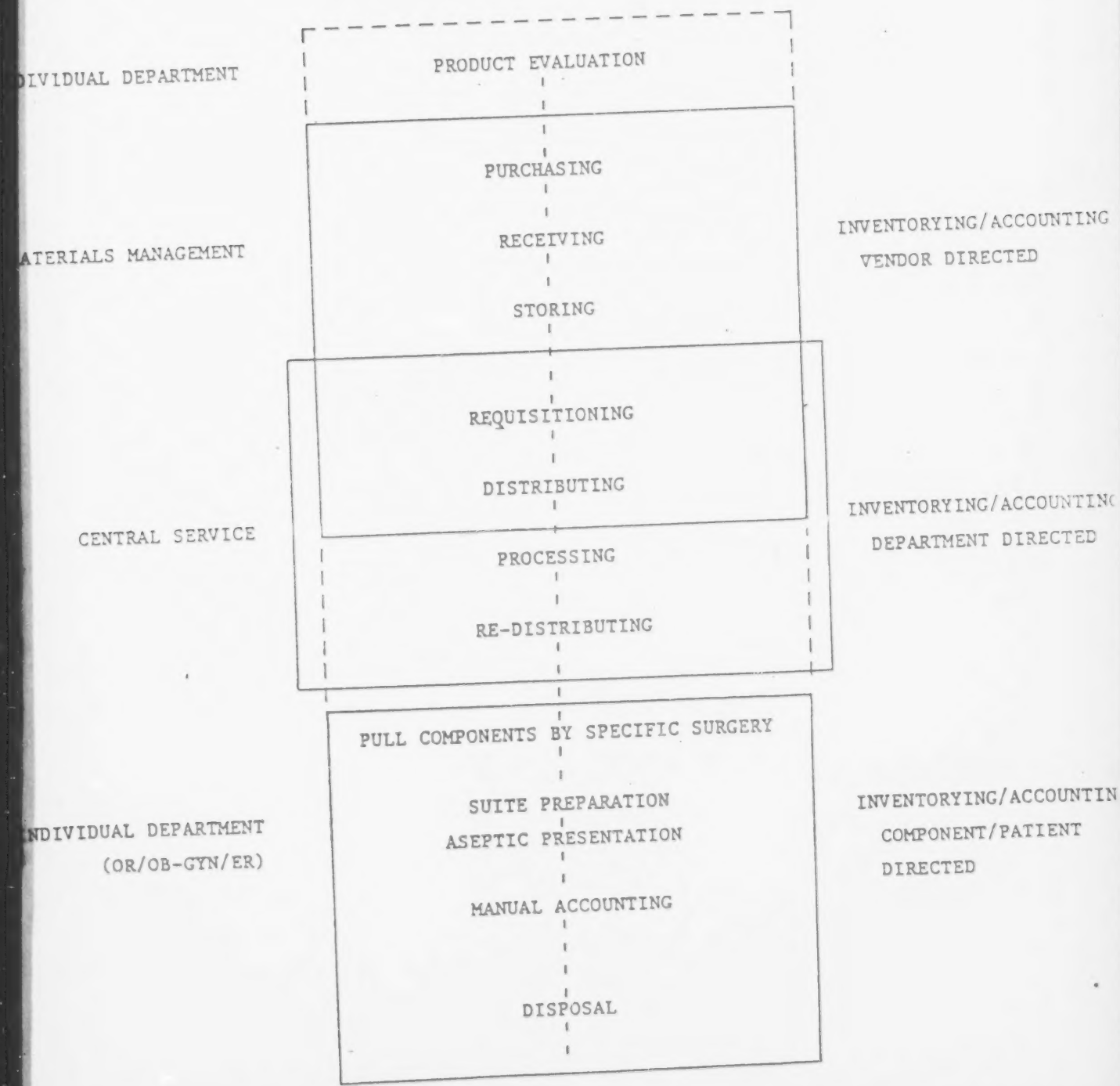
As companies like ourselves grow and command a larger share of the supply market, more and more direct manufacturers will compete for our business. By buying more cost-effectively from the original sources

(nonsterile bulk goods), our company will be in a position to offer the hospitals much more competitive prices.

The customized procedure tray service is only at its embryonic stages. Realization of its true potential could create a multibillion dollar market.

Figure 17-1

DISPOSABLE MEDICAL-SURGICAL PRODUCTS FLOW CHART



VIGNETTE #18
ESTABLISHING AND BUILDING A NEW COMPANY: THE EXPERIENCE OF METATECH CORPORATION

Thomas P. Carney, Ph.D.
President
Metatech Corporation
Northbrook, Illinois

After having spent 35 years with major companies in the pharmaceutical industry in jobs ranging from bench chemist to executive vice president, I decided in 1978, as so many others had decided before me, that it was now time to become my own boss and to do only those things that I wanted to do. Accordingly, I established Metatech Corp. with the not too modest or restrictive mission of "developing products based on high technology." Because of my background, it was probably inevitable that most of my interests would be in products related to medicine, although we do have several products that do not fall into this category.

One of the advantages of starting from ground zero in a new endeavor is that one is not restricted by any business orthodoxy. Some of the policies that I established for Metatech were required for the operation of any business. Others were not.

My first decision was never to work on a new drug. No entrepreneur can afford to enter the drug field when even the largest pharmaceutical companies have difficulty justifying the expenditure of $50 million or $60 million and 8 to 10 years in time before a decision can be made that a product is forthcoming and will be approved by regulatory agencies.

Rather than drugs, the logical target seemed to be medical instruments and devices. The market for these products is huge and growing. Yet the research and development (R&D) needed to find new instruments and devices does not compare either in quality or in quantity with that needed for new drugs. Federal regulatory requirements are strict, which is an advantage for a quality company with quality products. However, standards for instruments and devices are relatively easier to meet, because, for the most part, they depend on mechanical efficiency of the product rather than on a physiological reaction in a patient.

I decided that during the initial phase of Metatech's development, I would not build up an internal research staff. The first dollars spent by a company for research are usually devoted entirely to new and creative projects. As a company grows, however, more and more money is spent protecting what has already been developed. In addition, an internal research staff is built up and has to be kept busy. It sometimes happens that when a research project is finished by a company's internal research staff, the next problem is not one that the research staff is best qualified to solve. Since research staffs are never fired, the only option is to allow the existing staff to continue to work along lines of their own interests, while hiring additional staff to enter new areas.

In my own experience, I had developed contacts with R&D groups throughout the world, so I thought I knew where to find the best talent to solve any specific problem. To meet Metatech's requirements without building up an internal research staff, I decided to do all our work through outside contracts. Thus, when a problem was solved, the research group would no longer exist as an overhead for the company. In practice, this approach has worked very well. Projects for Metatech have been worked on in England, Israel, Japan, Germany, and Belgium, as well as here in the United States.

Another decision I made for Metatech was that we would not develop a product unless it was either unique or demonstrably superior to anything available. I was not interested in competing with established companies for established products. Obviously, there had to be a need for whatever product was developed. This requirement is one to which I was sensitive, because I had seen the development of many highly technical products that were technological successes but market failures. In the medical field, there are more than enough challenges to provide useful products that are also profitable.

I also decided that we would not try to sell a product until it had been developed through at least the final prototype stage and preferably through production. I had been on the other side of the table buying products and technology for large companies for many years, so I thought I knew what would be required to sell a product. For the most part, it is impossible to sell a concept. It is difficult to sell a product if there is more research needed to bring it to a conclusion. Most companies are not qualified to evaluate research. Research means risk, and established companies don't like risk.

The method by which Metatech's products would be sold was an important factor in deciding which products would receive the first development. Several methods of marketing could be projected. We could manufacture the product ourselves and sell it to an established company, sell it through distributors, or sell it directly to the consumer. We could develop and patent the product and then license other companies, or we could develop, patent, and sell the patent.

The first group of products we selected for development at Metatech were those that could be manufactured internally. These products were not necessarily end products in themselves, but could be sold as part of a kit containing already available products or greatly improved components of an already established product. An advantage of developing such products is that the customers are limited and readily identified. The second group of products we selected for development were those that, for an individual product, are entree to a very large market dominated by a single company. These are obviously candidates for licensing, since a startup company could not compete in the market.

I had set a time limit of 5 years during which Metatech would develop a line of products that could then be sold through any of the channels mentioned previously. How successful has this effort been? Metatech now has 21 products available for promotion and sale. All of them meet the criteria that I established originally. Eleven patents have already been issued, and we have 16 patent applications pending. A long list of potential products awaits future funding.

Where did these products originate? They came from both inside and outside the organization. The problem is not in finding good potential products. It is in selecting from among the almost unlimited opportunities those that best fit into the company objectives. Simply spending a few days becoming acquainted with hospital procedures will supply enough ideas for needed products to occupy R&D efforts for a good length of time.

A few examples will illustrate. Patients who have undergone procedures involving the insertion of an endotracheal tube typically complain of a "sore throat." When the endotracheal tube is inserted, a small balloon at the lower end of the tube is inflated to seal the passage so that gas inserted through

the tube cannot escape through the space between the tube and the trachea. The inflation of the balloon is performed with an ordinary syringe. Since the physician cannot see the balloon, the inflation pressure must be determined by feel and experience. Since the seal must be secure, the physician's tendency is to overinflate rather than underinflate. Thus, the patient's sore throat is not actually a sore throat, but an irritated trachea, caused by the pressure of the balloon against the wall.

To address this problem, we set ourselves the task of developing a simple system that would allow for the determination of an inflation pressure that would seal the passageway without causing irritation. The result was Metatech's pressure-indicating syringe, an ordinary syringe that indicates either qualitatively or quantitatively when there is back pressure during any inflation or injection. The syringe can be made in any size or shape conforming to the present syringe market.

I mentioned that we had set out to develop a simple method of controlling the pressure. The word "simple" is important. Next to discontinuing an ongoing research program, the most difficult thing in the world is to change an established routine medical procedure. The pressure-indicating syringe does not change any procedure. It looks like and is used like any syringe. Therefore, an advantage can be claimed for its use without changing any habits.

An important consideration for any R&D entrepreneur is the exploitation of any new idea. Although the pressure-indicating syringe was developed for a specific purpose, it was apparent that the principle could be applied to may procedures. Hysterisalpingography, the procedure for determining whether a patient's fallopian tubes are blocked, for example, depends on filling the patient's uterus with a radiopaque liquid, then determining by radiography

whether or not the liquid has flowed into the fallopian tubes. The radiopaque liquid is inserted in the patient's uterus by means of a large syringe. The procedure can be painful if too much pressure is exerted, and, of course, it could give a false indication of blockage if not enough pressure is used. The use of the pressure-indicating syringe would eliminate both of these problems. Spinal injections would also be an ideal situation for the use of the syringe. In fact, it is important to know in any injection whether or not there is back pressure caused, for example, by a plug in the needle. The pressure-indicating syringe could prevent accidents caused by a sudden surge of liquid. Thus, it could be argued that the pressure-indicating syringe should be used for every injection. Again, no procedure would be changed.

Metatech's interest in endotracheal tubes turned up three other product possibilities in addition to the pressure-indicating syringe. One of these was a swivel connector. An endotracheal tube is attached by means of an adaptor to the tubes through which the various gases flow, and in some procedures, it is desirable to be able to move these tubes into different positions. A swivel connector to be attached between the adapter and the gas tube was developed to allow rotation of the tubes from side to side. The swivel included a port to allow for evacuating mucus from the bottom of the tube without taking the patient off the gas system. Further, the connector was of such design that turbulence is completely eliminated during gas flow.

Another product resulting from our interest in endotracheal tube procedures was the bite block. This is a device that fits over the adapter of any endotracheal tube and prevents the patient from either chipping teeth from biting on the adapter if the tube is too short or from occluding the tube if the tube is too long.

Finally, we designed a totally new valve for use in the endotracheal tube system. The valve itself, because of its unique features, has found a number of uses for other medical instruments, and industrial uses are being investigated.

Thus, from an interest in eliminating "sore throats," Metatech has developed four new products. These four products illustrate the kinds of items we demanded initially--products we could manufacture ourselves if necessary, products that could be sold in a number of different markets, and products for which there was a need.

Interest in microsurgery brought Metatech further up the technological ladder. Several years ago, the Food and Drug Administration (FDA) discovered that microclips used to seal off small vessels during micro and other surgery could cause serious damage by cutting through the vessel if the force of the clip was too great or could slip off if the vessel was not strong enough. FDA issued a contract to a university biomedical department to design a machine that would measure the pressure a clip exerted when it was in use. It had been discovered that clips change pressure following use and sterilization, so the machine would be used to determine the pressure before each use.

Working with one of the country's outstanding neurosurgeons, Metatech also set out to develop such an instrument. The resulting clip-testing instrument not only determined the pressure exerted at a preset opening, but also gave a complete calibration, indicating pressures when the clip was used on different sized vessels and also when the jaws of the clip were inserted to different depths.

As a result of the development of the clip-testing instrument, Metatech became interested in the entire microsurgical field. The surgeon with whom we had worked had done some pioneering investigations showing that when a clip

exerts pressure on a vessel, in some cases, the intima (the inner lining of the vessel) is damaged, and the results of the damage do not show up for several weeks after the operation has been completed. My own interest in developing the clips was influenced somewhat by the fact that when we had to buy clips for testing on the calibration instrument, we found the least expensive clip cost $45 and other prices ranged to above $100.

Metatech saw several opportunities here. First, we developed a clip that exerted a pressure--as low as 5 grams--lower than any other clip available. We then developed several adjustable clips, so that the pressure could be regulated. The advent of nuclear magnetic resonance imaging as a medicinal diagnostic tool made it imperative to have available nonmagnetic clips. If a patient with an implanted metal clip were subjected to nuclear magnetic resonance, the magnetic force would cause the clip to move, in most cases creating life-threatening situations. We therefore developed a duplicate line of plastic clips. Metatech's entire line of clips--plastic and metal--can be produced at a fraction of the cost of other currently available clips.

Another problem that surfaced during our examination of microsurgery was the possibility that small vessels--arteries, veins, nerves--adjacent to the site of an operation could become damaged accidentally. At the suggestion and with the cooperation of a Canadian microsurgeon, Metatech developed a vessel protector. This is a device that fits around a tiny vessel to shield it from scalpel or laser damage. The same device, when made in different colors, can be used to color code vessels. For example, if a tiny vein is to be severed and then rejoined, the ends can be identified by means of the colored vessel protector. An offshoot of the vessel protector is a device to be placed, either temporarily or permanently, around a weak spot in an artery or vein.

One of the most time-consuming procedures in microsurgery is suturing small vessels. A device has been developed to tie the suture automatically.

A final example of how developments occur when problems are sought out is the experience with our transducer. It was brought to our attention by a neurosurgeon that damage to the brain sometimes occurs during brain surgery when the surgeon uses a retractor to move the brain into various positions. Thus, there was a need for the development of an instrument to measure the pressure exerted by the retractor during actual use. Working with a brilliant young bioengineer, who is also responsible for the clip developments and who is now part of Metatech, we developed such as instrument. But during the course of this work, discoveries were made that resulted in a tremendous advance in transducer technology. As a result of this investigation, we now have a means of determining pressure, temperature, movement, and rate of flow. Further, the information is determined and transmitted by and through a monofilament as small as 0.01 inch. The Transducer has a wide range of uses--for determining blood pressure continuously when inserted into a vessel, for determining blood flow and temperature. It is nonelectrical and can therefore be used in environments that require explosion-proof conditions. It has an equal potential for industrial use in strain gauges, for determining temperature, and in communication systems.

Metatech's experiences with endoctracheal tube, microsurgery, and the transducer illustrate how entrepreneurs in R&D can think and plan. Such planning might seem to be "stream of consciousness." I prefer to think of it as "stream of opportunity." The experiences cited also illustrate two great advantages entrepreneurial companies such as Metatech have over large established companies--namely, flexibility and accessibility.

A small company can make decisions instantly. With the stipulation that a product be unique or superior, that there be a need for it, and that it be profitable, Metatech can follow any lead. It is not constrained by restrictions of "company policy" or "product lines." I believe more good ideas have been rejected for the reason that "it doesn't fit into our product line" than for any other reason. But a new idea is a very precious thing. It doesn't come around too often, and unless a company is prepared to take advantage of every new idea, it is not being totally efficient.

The second advantage a small company like Metatech has is accessibility to anyone with a product or idea. One of the unfortunate results of the desire of a large company to protect itself against law suits by inventors, and the desire of the inventors to protect themselves from being cheated by the company, has been the erection of a legal screen preventing communication. The fear of the company is that an inventor will submit an idea of product and have it rejected, and then, some time in the future, see the company produce the same of a similar product claiming it as its own. The natural tendency is for the inventor to sue. In very rare instances, such dishonesty might occur. However, it is more usual for a company with a large research staff to have anticipated the idea with its own organization.

Another legal requirement is that the inventor sign a "confidential disclosure agreement." Is it any wonder that inventors think they are not loved by large companies when they are asked to sign agreements that include such statements as: "It must be clearly understood that Company X assumes no obligation to you whatsoever in connection with any information you may disclose to us."? The company interprets such a statement as simply protecting itself. The inventor interprets the statement as meaning that the company can do anything it wants with the information supplied by the inventor

without any reward to the inventor. When the paranoia of the inventor (in inventors, it is an inherited gene trait) is reinforced by the paranoia of the company (in companies, it is an acquired characteristic that comes with bigness), there is not much chance for an exchange of ideas.

We have not experienced such mutual distrust. Over the years, it has been my policy to listen to any inventor. I have wasted a lot of time, but I have also received a lot of good ideas and built up a lot of good will. Possibly an extreme example of the benefits of tolerance is the method by which Metatech acquired the rights to a device for purifying water without the use of external light, including sunlight. The process was invented by a London taxi cab driver, who described his invention on a drive from the airport to the city. We carried out an investigation, and the acquired the total rights to the invention. Small prototypes were operated in the English Channel and off the coast of Haifa. The process has been patented all over the world, particularly in those countries with desert lands adjoining the sea. This is one of our few ventures outside of the medical field.

With Metatech's reputation of having a sympathetic approach to inventors combined with our track record of developing inventions, we continue to receive a stream of products at all stages of development from conception through prototype.

I have not mentioned the first hurdle that an inventor or entrepreneur must overcome, namely financial support. Partly from choice, partly from necessity, I financed Metatech with my own money. At the beginning, I made a few half-hearted attempts to interest outside investors in my company. However, I had no sales or profits, so there was a risk connected with the operation, and I soon found out that venture capitalists were really not interested in venturing. I therefore decided to finance my own work, to make

my own mistakes in private, but also to have the total freedom to do anything I wanted to do.

After having developed some 20 products, I again sought outside investors. In March of 1983, I obtained sufficient investment capital to establish the organization necessary to market the products.

I started this essay by saying that I decided to be my own boss and to do only those things I have wanted to do. I have been my own boss, but I have not been able to do all the things I wanted to do, and I did find it necessary to do some things I didn't want to do. Occasionally, I think back to the days when I could work a normal 12-hour day and depend on someone else to do important things like making the coffee. These occasions occur only rarely, and do not last long. Two major hurdles--financing and development of products--have now been overcome, and preliminary sales contacts and some sales have been made.

I might even start to build an internal research organization.